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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/04	A1	(11) International Publication Number: WO 00/09008 (43) International Publication Date: 24 February 2000 (24.02.00)

(21) International Application Number: PCT/US99/18172

(22) International Filing Date: 11 August 1999 (11.08.99)

(30) Priority Data:
09/135,249 17 August 1998 (17.08.98) US

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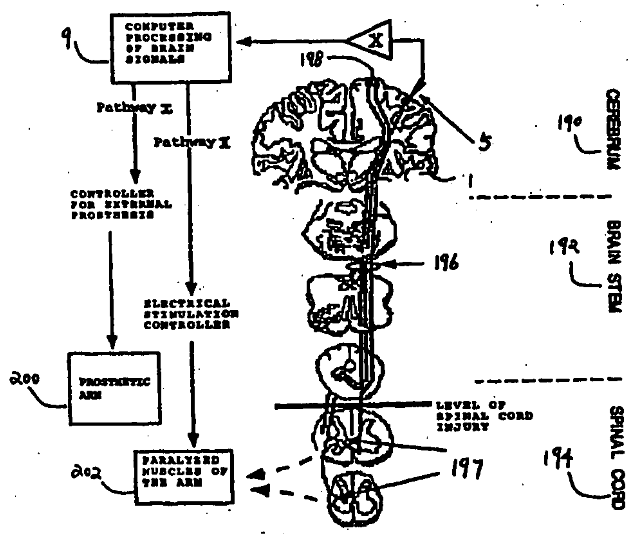
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYSTEM AND METHODS FOR CONTROLLING DEVICES BY BRAIN SIGNALS



(57) Abstract

A system and method control prostheses (200), other devices with signals received by sensors, implanted directly in the brain or other parts of the nervous system of a subject, and transmitted to an external receiver. Included in the system are sensors (5) in the form of bundles of small, insulated, flexible wires (10), configured in a parallel or twisted array, which are used to receive multicellular signals from small clusters of neurons. A new "calibration/adaptation" system is developed, in which the neural signals are cross-correlated with the parameters of a set of standardized or model movements as the subject/patient attempts to emulate the model movements, and on the basis of the correlations the neural signals that are best suited for control of the corresponding movement or movement parameter of the external devices are selected.

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SYSTEM AND METHODS FOR CONTROLLING DEVICES BY BRAIN SIGNALS

This invention relates generally to systems, methods and devices for interfacing between nerve cells (neurons) and external devices and, more particularly, to systems, methods and devices for extracting signals directly from the human brain and nervous system for use in the control of external devices.

BACKGROUND OF THE INVENTION

The human brain is an exceedingly complex processing system, which integrates continual streams of incoming sensory input data with stored memories, uses the input data and memories in complex decision processes at both conscious and unconscious levels, and on the basis of these processes generates observable behaviors by activation of its motor or movement control pathways and the muscles which these innervate.

In certain cases of traumatic injury or neurological disease, however, the brain is partially isolated from the periphery. Input data from certain senses are thus lost, at least for a portion of the body, as are many voluntary movements. Spinal cord injury is a well known example. With spinal cord injury, the pathways that link higher brain regions with the spinal cord and that are used for control of voluntary movements may be functionally transected at the site of injury. As a result, the patient is paralyzed, and (s)he can no longer voluntarily activate muscles that are innervated by regions of the spinal cord below the level of the injury. Despite the injury to their long fibers, however, many of the cells in these higher brain regions that control voluntary movement will survive and can still be activated voluntarily to generate electric signals for controlling voluntary movement. By recording directly from these cells with implantable devices (e.g., electrode arrays), signals generated by the cells may be "exteriorized" and used for the control

of external prostheses, such as an assist robot or an artificial arm, or functional electrical stimulation paralyzed muscles.

Another example of such loss occurs in cases of amyotrophic lateral sclerosis (Lou Gebrig's Disease), in which the motor neurons which control muscles, as well as some of the brain cells that control these motor neurons, degenerate. In advanced stages of this disease, the patient may have completely intact senses and thought processes, but is "locked in", so that neither movements nor behavioral expressions of any kind can be made. Providing these patients with some way of communicating with the external world would greatly enhance their quality of life.

In sum, there is a need to develop a system for monitoring and processing the electrical signals from neurons within the central nervous system, so that the brain's electrical activity may be "exteriorized" and used for the voluntary control of external prostheses or assist devices. In this way, damaged pathways are circumvented and some control of the environment can be restored. Because the electrical fields of small groups of neurons drop off rapidly with distance from the cells, this system should include surgically implanted "tiny" electrodes or sensors, which can be placed in close proximity to the cells that generate command signals for voluntary movement.

Earlier attempts to utilize signals recorded directly from neurons for the express purpose of controlling external prostheses have, however, encountered a number of technical difficulties. A major problem is how to obtain stable electrical signals of sufficient amplitude for real-time control of an external device. Two previous approaches have been used, but neither is successful in this regard.

In the first approach, microelectrodes with small tips (< 300 em sq. surface area) have been used, which are positioned to within 10-100 em of a single neuron, thus isolating its action potentials or "spikes" from that of other, more distant cells. In some cases, two or three adjacent neurons are recorded from simultaneously. In such cases, electronic devices are used to discriminate between the spikes of the individual cells and to sort their "spike

trains" into distinctly recognizable signals. One problem with this approach, however, is that the effective "isolation" of the spikes of only one to a few neurons requires that the recording electrode be positioned in close proximity to the neurons. Thus, to obtain such records from a sufficient number of movement-related brain cells, scores of electrodes should be implanted in the hope that a few of them will be in just the right position to record signals from one or only a few movement controlling cells. Given the required proximity of the electrode and the cells, there is a high probability, however, that small movements of the former with respect to the latter will result in signal loss either because the electrode moves slightly away from the cells of interest, or closer to them, resulting in cellular injury. With blood pressure induced pulsations of the brain within the skull, such relative movement is not only possible but very likely.

In recent years, small, multichannel, micromachined (integrated circuit) electrodes have been developed for use in neural recording. Given sufficient recording channel density, these electrodes promised a partial solution to the electrode/tissue movement problem described above. If the signal was lost from one channel by electrode movement, there was hope that it might be "picked" up by an adjacent channel, which moved closer to the active neuron at the same time that the previous one moved away. However, problems have been encountered with these electrodes as well. For reasons that are not entirely clear, neural signals are lost from these electrodes over time, due apparently to the formation of polarization potentials at dissimilar metal junctions along the recording channel, or the ensheathment and thus biological insulation of the electrode by glial cells.

A second approach is to use electrodes with larger exposed recording surfaces (in the range of 0.5 to 1.5 mm sq. surface area). These low impedance electrodes have lower noise characteristics than those with smaller tips, and can reliably record the activity of hundreds to thousands of neurons at greater distances than can the latter. Indeed, low level electroencephalographic (EEG) or field potentials can even be recorded from the surface of the scalp. This approach thus can avoid the difficulty of

different signal output levels caused by small movements between the electrodes and the selected cells encountered in the first approach. The use of the signals recorded in the second approach presents, however, a major problem for prosthesis control. In such recordings, the desired control signals may be of very low amplitude and may be "buried" within, or confounded by, EEG potentials from neurons that are not involved in voluntary motor processes. Thus, averaging must be used over many movement attempts to extract a usable signal. For this reason, this approach is less than desirable and perhaps not useful for real-time neural control of an external device.

Another problem, which occurs regardless of the electrode type used, is that neural signals may change over time for a variety of reasons: e.g., (a) naturally occurring cell death, which occurs randomly throughout the brain in adults; or (b) learning processes, which may, over time, alter the quantitative relationship between a neuron's activity and the external parts of the body to which it contributes voluntary control.

SUMMARY OF THE INVENTION

The present invention overcomes some of the difficulties described above with improved as well as new systems, methods and devices for obtaining signals directly from the brain or central nervous system, and for processing and utilizing these signals to control external devices. The systems described here are adaptable to a variety of signals from the brain or central nervous system as diverse as a) neurally generated electrical signals, recorded with microelectrode technologies from within the brain or with surface electrodes from extracranial sites; and/or (b) measures of localized blood flow that are correlated with neural activity, if techniques for miniaturization of current devices for making such measurements, in real time, are developed in the future. The external devices may include any device that can be controlled by processed electrical signals. These devices include, but are not limited to, artificial or prosthetic limbs; computer controlled. functional electrical stimulation of muscles of paralyzed individuals

for the restoration of movement; robots or robotics components; computers or computer displays; or the teleoperation of robots and machines in hostile environments.

A preferred embodiment of the invention represents a unique blend of technologies from the fields of neuro- or electro-physiology, biomaterials science, neural signal processing, functional brain imaging (to guide implantation of sensors), and robotics or prosthetics. Included in the embodiment is a unique recording arrangement with bundles of six to ten small (20-50 μm in diameter), insulated, and flexible, noble metal wires that are arranged in a parallel or twisted array. The wire bundles are constructed so that each recording wire can collect multicellular signals from a small cluster of neurons, with tips that are incremental in length, so that many recording sites can be sampled along a single line of bundle insertion into the brain.

According to another preferred embodiment, software routines, together with corresponding hardware, are used to perform specific signal correlation, adaptation, and distribution as part of a general recalibration procedure. A unique signal processing method is provided to convert recorded neural signals into a resultant signal that is useful for control of an external device. And, for the first time, the disclosed system incorporates neural net software routines to map actual neural signals onto desired movement functions.

In accordance with a preferred embodiment of the invention, a robot arm is controlled by the neural signals recorded directly from the voluntary movement (motor) control areas of the cerebral cortex of a subject, such as an alert monkey. It can be appreciated, however, that the concepts and general procedures of using neural signals to control movements of a robot arm, as described in the various preferred embodiments of this invention, are valid for the control of any external device that can be manipulated directly or indirectly by electrical signals and are not limited to use with monkeys or other trained animals. The followings are the devices and stages of signal processing system implementation in a particular preferred embodiment of the invention.

(1) Sensors (e.g., electrodes) and Sensor Arrays

Sensors and sensor arrays used in a preferred embodiment of the present invention should have appropriate geometry and size for the configuration of the neural implantation site, and the methods of construction of the wire bundles used in this embodiment allow such flexibility. In the present invention, these sensors are comprised of miniature, multichannel microelectrodes, either (a) fabricated with micromachining/photolithography methods, or (b) from noble metal (e.g., platinum or Pt) microwires, oriented along a single axis in a parallel or twisted array. For example, for extraction of signals from the "arm" control regions of the cerebral motor cortex of a human for the purpose of rudimentary control of a robot arm, an estimated minimum of 16-24 recording channels would be needed, with an electrode density of about 24/cm sq. Further, the implanted electrodes and arrays should be tailored to the required geometry of the implantation site, so that the electrode recording tips contact the correct cellular regions. The precise locations and shapes of the correct cellular regions can be determined prior to implantation by magnetic resonance imaging (MRI) and other brain imaging procedures. Multisite recording from cells with these regions is best accomplished by a wire bundle electrode array, with the recording tips of the bundled wires located at 0.5-0.6 mm intervals along the shaft of the array. When inserted normal to the cortical surface and aligned with cortical lamina V in the anterior bank of the central sulcus, this electrode array can sample activities from several clusters of the cortical output neurons that would normally control arm/hand movements. Because the wire bundle electrodes are made of a single noble metal, they do not suffer the loss of signals due to polarization potentials at dissimilar metal interfaces, as occurs in the micromachined electrodes constructed to date. Moreover, because the exposed (non-insulated) surface area of the wire electrode recording tip (400-1800 μm sq.) is larger than that typically used in an electrode designed for isolation of single neurons (150-300 μm sq.), signals can be recorded with the tips at a greater distance from the cells of interest, thus reducing the

probability of cellular injury by relative movements of the electrode with respect to brain tissue.

(2) Electronic Microchips

According to one aspect of the preferred embodiment, electronic microchips are needed for various purposes, such as amplification, filtering, multiplexing, and radio transmission of signals to external receivers. In the examples given below, preamplification of multiple channels of neural data, multiplexing of neural data from multiple channels into a single data stream, and radio transmission out of the body of a subject would be accomplished by chips coupled to the electrode array, that are on the order of 2 x 2 cm sq. or less in size.

(3) External Receivers and Demultiplexers

According to another aspect of the preferred embodiment, external receivers and demultiplexers are needed for allowing the exteriorized data stream to be detected and reseparated into separate neural data channels, which can then be individually selected and mathematically transformed for control of specific devices (e.g. an arm prosthesis) or device components (e.g., separate parts of the arm prosthesis).

(4) Signal Usage, Correlation, and Adaptation Methods

Once the neural signals are exteriorized, the most appropriate use for each should be determined. For example, if signals are derived from the "arm" area of the motor cortex, some of the signals are related to shoulder movements, others to movements about the elbow, some others to movements about the wrist, and the rest to finger movements. (In the paralyzed individual, of course, the movements are "attempted" rather than actual voluntary movements.) If the signals are not derived from the motor cortex but are still under voluntary control by the subject, and are to be used for control of arm prosthesis movements, a determination should also be made as to which are the most useful signals for fine hand control, which for upper arm control, and so forth.

Recorded neural signals may also change over time, due to electrode "drift" within the brain tissue (so that the electrode moves away from some

cells and closer to others), natural death of cells (50,000-100,000 cells/day in the adult brain), or changes in the parameters of cell discharge in relation to movement which result from motor learning. Consequently, a procedure according to the invention adapts to, or partially compensates for, changes in recorded neural signals and their parameters over time, so that the same implanted electrode array is useful for control purposes for as long as possible.

A general neural prosthesis calibration procedure, including newly conceptualized signal correlation, adaptation, and distribution (software) routines, accomplishes all of these goals. In this procedure, the subject observes a set of simulated arm movements (or other activities) on a computer screen, and attempts to "track" or emulate these same movements with attempted movements of his/her own (paralyzed) arm. During the emulation process, the activity on each neural channel is cross-correlated with selected parameters of the simulated motion (joint rotation, position of the hand in space, speed of movement, etc.), to determine with which it is most highly correlated. The activity of this most correlated channel is then "routed" or "distributed" to the circuit which controls the device component or movement parameter with which it is most highly correlated. Since this calibration procedure can be performed readily by the subject or patient on a periodic basis, the optimal neural channels for control of the external device can be reselected and redistributed each time, thus providing a continuing adaptation to changing neural signals, regardless of the cause of these changes.

(5) Shaping of Signals for Optimal Device Control

Once a subset of signals has been selected for control of an arm prosthesis (or other device), according to one aspect of the preferred embodiment, the signals should still be mathematically combined for optimal control of that device. For example, if neural signals "x and y" out of some larger set of signals correlate well with attempted hand movements about the wrist, and they are to be used for that purpose in controlling an arm prosthesis, they should still be mathematically processed to optimize such

control. By "optimal", it is meant that the processed signals should drive movements about the artificial wrist that match as closely as possible those model movements that are observed by the subject during the calibration procedure. To accomplish this, software networks are used for mapping actual neural signals onto desired movement functions; in the example referred to here, these would be the simulated arm/hand movements observed by the subject on the computer screen.

Accordingly, it is an object of the present invention to provide an improved system for recording neuronal signals directly from the brain or central nervous system for external device control.

It is another object of the present invention to develop an improved system which can be used with signals derived from small sets of selected single neurons, whose signals are separated from those of other nearby cells with electronic "spike" discrimination methods and are then recombined into a composite control signal.

It is a further object of the present invention to provide an improved system which can also be used with signals derived from small sets of neurons (2-10), whose signals are simply summed and electrically processed to obtain a useful signal for external device control.

It is yet another object of the present invention to provide multi-electrode sensors for recording from small clusters of neurons and providing signals that are midway between those obtained with the single neuron and EEG recording approaches described above.

It is yet a further object of the present invention to provide multichannel connectors and recording systems for use with the multi-electrode sensors.

It is also an object of the present invention to provide data reduction methods for converting the electrical activity signals recorded from clusters of neurons into useful intermediate control signals.

It is also another object of the present invention to provide an application of Neural Net algorithms for relating the intermediate control signals to movement parameters.

It is also a further object of the present invention to provide a novel calibration and adaptation method for periodically rematching recorded signals to the desired movements of an external device, so that compensation occurs for fluctuating signal amplitudes and/or motor learning.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and form a part of the specification, illustrate preferred embodiments of the present invention and, together with description, serve to explain the principles of the invention. In the drawings:

FIG. 1 is an exemplary diagram of a system according to the present invention for use by a subject with a spinal cord injury in voluntary controlling an external device.

FIGS. 2 (A) to (C) are schematics of sensors (electrodes) and sensor arrays according to the present invention for recording brain activity.

FIGS. 3 (A) and (B) are photomicrographs of recording arrays of the present invention used to monitor the activity of sets of cortical neurons.

FIGS. 4 (A) to (C) are diagrams of other embodiments of electrode arrays and methods for bringing power to and taking neural signals from an implantable microchip.

FIG. 5 is a diagram of an implanted device for externalizing neural signals for control of prosthetic devices.

FIG. 6 is a diagram of an implanted device according to a second embodiment for exteriorizing neural signals.

FIGS. 7 (A) and (B) are waveforms schematics of signals in the second stage of processing of recorded multiunit neural signals.

FIGS. 8 is a block diagram of a second stage of processing.

FIGS. 9 (A) to (E) are waveforms schematics of signals arising in the processing of multiunit recordings from the arm area of the sensorimotor cortex of a monkey.

FIG. 10 is a schematic of third and later stages of neural signal processing system, and an example of operation of the neural prosthesis for control of a prosthetic or a robot arm.

FIG. 11 is a diagram of operations performed by a movement calibration and signal distribution system depicted schematically in FIG. 10.

FIG. 12 is a schematic of an artificial neural net used to process neural input data before passing it to a peripheral device controller.

FIGS. 13 (A) and (B) are graphs showing examples of processed neural discharge and the real-time prediction of wrist position from this neural discharge by the artificial neural net of FIG. 12.

FIG. 14 is a flow chart showing steps used in calibrating the neural control system of FIG. 1, using as an example the control of an artificial limb or functional electrical stimulation of paralyzed muscles to produce a particular movement.

DETAILED DESCRIPTION OF THE DRAWINGS

Reference will now be made in detail to preferred embodiments of the invention, non-limiting examples of which are illustrated in the accompanying drawings.

A. Overview

With reference to FIG. 1, a system according to a preferred embodiment of the invention uses signals from cells in higher brain regions 1 can be activated voluntarily by a patient/subject, to in turn control external devices such as an artificial arm 200 and electrical stimulation of paralyzed muscles of an injured arm 202. FIG. 1 shows sections through various levels of the cerebrum 190, brain stem 192, and spinal cord 194. Also shown are pathways 196 that link the motor (movement control) areas of the cerebral cortex 198 with the spinal cord motor neurons 197 that control muscles of the arm 202. By recording directly from the cells in higher brain regions 1 with implantable devices 5 (e.g., electrode arrays), signals collected at the cells can, after processing by computer and electronic interfaces 9, be

"exteriorized" and used for the control of external prostheses, such as the artificial arm 200 (external pathway I) or the electrical stimulation of paralyzed muscles 202 (pathway II).

Alert monkeys that are trained to make specific arm movements in order to receive small food or juice rewards are used as subjects. Under surgical anesthesia and sterile conditions, arrays 5 of microelectrode sensors are implanted into the motor (voluntary movement control) areas of the animal's cerebral cortex 198, opposite the trained arm, preferably according to one of the methods as demonstrated in FIGS. 5-6. When the animal is fully recovered, signals from sets of neurons whose electrical activity is correlated in time with performance of these arm movements are identified, and the signals are processed mathematically for control of the robot arm as shown in FIGS. 7-11. This processing is such that the neural signals that are selected for control of a particular part of the arm (e.g., movements about the elbow) will, when applied to the controller for that part, produce robot arm movements that are very similar to those made by the animal. These "off-line" simulations allow of adjusting neural net parameters for optimal control of the robot arm as shown in FIG. 12. Again using positive reward procedures, the animals are then trained in 1 hour long daily sessions to adapt to the movements of the nearby robot arm, which their brain signals now begin to move roughly in parallel with their own arm movements. Delivery of the food rewards is then gradually made contingent not upon the accuracy of the animal's own arm movements, but upon those of the robot arm. Eventually, the animal's own movements can be temporarily restrained (by securing the sleeve of its training jacket), and he/she can obtain food solely through directly controlled movements of the robot arm with the neural signals recorded directly from his/her brain. The systems, methods, and devices according to various embodiments of the current invention can also be used by medical use with humans.

B. Sensors/Electrodes for Recording Neural Signals

Examples of the implantable devices 5 are shown in FIGS. 2 (A) to (C). FIG. 2(A) shows a preferred embodiment of sensors or a sensor array 5' according to the present invention for recording from cortical cells of a brain for extended periods of time. Six to ten small (25 to 50 μm diameter), insulated, noble metal, preferably Pt or Gold, wires 12 are bundled in a parallel or twisted array 10, with staggered length so that the exposed recording tips 14 end at different cortical depths (from the surface of the brain) when inserted into the brain.

In one embodiment of the invention, the wires 12 are constructed of 25 μm diameter Pt, insulated by a thin layer of Formvar, Isonel, or some other suitable material 15 obtained from the California Fine Wire Co. of Grover Beach, California. A completed wire bundle 10 made with 25 μm wire is approximately 75 μm in diameter. In another embodiment of the invention, the wires 12 are constructed of 50 μm diameter wire. A completed bundle 10 made with 50 μm diameter wire is about 150 μm in diameter, and is 15-35 mm long from electrode tip 14 to a connector assembly 50. Electrodes made with the 50 μm diameter wire isolate the electrical activities of small clusters of 3 or more neurons as well as those obtained with the 25 μm diameter wire.

The wires 12 are held in position with respect to one another by a light-cured optical cement bead 16, placed 6-8 mm from a most distant wire tip 142. The recording tips 14 of the individual wires 12 are located from 2 to 6-8 mm distal to the bead 16. The difference in length from one tip to its neighbor tip is substantially equal in one embodiment of the invention, about 0.5 to 0.6 mm, but these distances can be varied, depending upon the implantation site and its geometry. The bead 16, in one embodiment of the invention, is a small (0.5-0.6 mm diameter) drop of UV-curable acrylate, cured with 30 sec of UV exposure from a small, focused, UV gun. The cement bead 16 is also used for handling and manipulating the array 5' during its insertion into the brain, because of the bead's degree of rigidity. On the proximal side of the bead 16, the wires 18 separate to bundle loosely to the implanted connector

assembly 50 (see below). By inserting several staggered arrays 5' along the central sulcus of the cerebral cortex 198, where major motor areas exist, it is possible to place them all within the cortical layer that contains the corticospinal neurons that participate normally in the control of voluntary movement. MRI is used prior to surgery to locate this region precisely in relation to anatomical landmarks on the skull, thus guiding electrode implantation. Placement of eight to twenty of sensor arrays 5' in wire bundle form ensures recording from sufficient numbers of cells to capture a useful number of control signals.

An alternative type of sensor array 5" is shown in FIGS. 2(B) and 2(C), where the latter is an enlarged view of recording tips 14' shown in FIG. 2(B). In principle, the sensor array 5" is similar to the bundled wire array 5' shown in FIG. 2(A), except that in this case the entire array 5" is constructed by micromachining or photolithographic techniques. In the embodiment shown, each recording channel or "wire" 12' is a very thin (4-10 μm wide) strip of metal, left on a silicon substrate after etching away the surrounding metal. A long, sharp, insulating silicone substrate 11 contains six to eight separate recording channels 146, which end in uninsulated recording pads 144 at various sites along a sensor shank 13 which, when covered with a bead 16' of epoxy or similar material, can be used for gripping and manipulation (with fine tools) of the sensor array 5". Again, an enlarged bead 16' or disc region occurs along the shank 13. On the opposite side of this bead 16', separate (insulated) wire channels 18' course to a 1.0 mm diameter pad 50'. Though more desirable because of their small size and precise geometry, long-term recording was less successful with the micromachined sensor array 5" than with the sensor array 5' in wire bundles 10 described above and shown in FIG. 2(A). Reasons for this include micromachined sensor's greater fragility, difficulty in making connections with their channels, polarization potentials between their dissimilar metals which block electrode conductance, the encasement of the electrodes by glial cells, and insulating them from neural signals, when they are implanted.

Photomicrographs of the arrays 5' and 5" are shown in FIGS. 3 (A) and (B), respectively. FIG. 3(A) discloses a bundle 10 of pure platinum wires 12, insulated except at the tips 14. FIG. 3(B) shows a photo-lithographically prepared (micromachined) array 5". Thin, insulated conductors 12' travel from non-insulated recording pads 14' (just visible along the shank 13 of the electrode 5"), up a longer cable, and to a dispersed pad where electrical connections can be made.

FIGS. 4 (A) to (C) show yet other types of electrode arrays that may be used in the present invention. In FIG. 4(A), "n" parallel electrodes 12", each 2.5-3.0 mm in length, protrude from a silicone wafer 20 as an insulating substrate, each in electrical continuity with a gold contact pad 30 on the opposite surface of the wafer 20. The electrodes 12" are insulated except at the tips 14". Each of the electrodes 12" can be made from a short length of 90% Pt and 10% iridium wire or other noble alloy, which has sufficient stiffness over its short length to allow penetration of the pial covering of the brain and insertion into the cerebral cortex. An electrode array 25 of this type with each electrode 12" being a platinum plated silicon probe, but not in bundle form, is commercially available. As shown in FIGS. 4(B) and 4(C), an electrode array 25, as shown in FIG. 4(A), can be bonded to a second microchip 40 that contains "n" pads that mate precisely with those on the electrode array 25. The microchip 40 and the electrode array 25 are bonded in close contact and are then hermetically sealed. The microchip 40 may contain integrated circuits 42 that provide for amplification of the signals in each of the n electrodes or channels, and for multiplexing these signals into a serial data stream for transmission out of the brain 1. The microchip 40 and electrode array 25 set upon the meninges 3 (tissue coverings of the brain 1), but beneath the skull (not shown), and the electrodes 12" penetrate the meninges 3 into the substance of the brain 1 so that neural signals can be directly collected therefrom. The electrodes 12" which protrude from the array 25 may be individual wire leads, or short bundles of the type described above.

FIGS. 5 and 6 illustrate two possible ways that the signals may be led from the brain 1 to external processing units. The first is a communication channel established by a hardware connection as shown in FIG. 5, and the other is a communication channel established by a wireless mechanism as shown in FIG. 6.

Referring first to FIG. 5, in connection with FIG. 4(B), the implanted electrode array 35 has the first stage electronics circuitry 42 for signal processing (multichannel amplification and multiplexing) attached. Signals from the circuitry 42 are sent via a small, flexible cable 51 to a second stage device 7 implanted within the skull 2. An implant/skull junction 8 is hermetically sealed. This device 7 relays power from an implantable battery pack 56 connected to it by leads 52 beneath the skin and scalp 4. The implanted electronics 51, 7 and 42 are preferably programmable and contain circuitry for selecting (gating on) the neural channels to be used and for setting other recording parameters. They also preferably contain a transmitter for relaying the neural signals by RF signal to a receiver, which in turn relays it to demultiplexing and the later stages of neural signal processing described in more detail in the subsequent text and figures.

Referring now to FIG. 6, in connection with FIG. 4(C), there is shown an alternative implant method, according to a preferred embodiment of the invention, which uses a wireless mechanism, thereby allowing the cranium (skull) 2 to be reclosed, and thus reducing chances of infection. The electrode implant array 45 contains the microchip 40 which has multichannel amplifiers, multiplexing circuitry, and an RF transmitter. Attached to the microchip 40 are two coils 53 and 54 (as shown in FIG. 4(C)). One coil 53 allows power to be transmitted to the implant array 45 via a coil in an external unit 47 by induction, and the second coil 54 allows transmission of the multiplexed, multichannel neural signal out as a serial data stream. The external unit 47 contains a power coil, and a chip for conversion of DC voltages into the AC voltages that are necessary for inductive coupling to the internal coil 53. All devices are implanted beneath the skin. Battery packs 56 and the external unit 47 can be changed by simple surgical procedures if

necessary. With the technique shown in FIG. 6, the skull 2 is closed completely. While coils are used to describe the way that signals are led from the brain to external processing units by a nonresonant wireless mechanism, other kinds of devices, such as LC circuits or low pass filters, can be utilized to establish a resonant wireless mechanism to relay the signals as well.

Both techniques shown in FIGS. 5 and 6 allow for complete implantation of the first stages of the system. In the first method (FIGS. 5 and 4(B)), a junction 8 is hermetically sealed between the cranial implant site 51 and the second stage device 7. In the second method (FIGS. 6 and 4(C)), the skull 2 is resealed completely. In both cases, surgical removal and updating or replacement of implant components is possible if necessary.

When these electrode arrays and devices are to be implanted in humans, functional MRI (fMRI) technology may first be used to identify those brain regions that the patient still has under voluntary control, thus allowing precise, functional placement of the implants and the recording electrodes.

C. Second Stage Processing of Neural Signals

The types of neural signals recorded with the electrode technologies described above are shown schematically in FIGS. 7(A) and (B). Typically, the recorded neural signals include action potentials or "spikes" (brief, voltage transients) which signal the discharge of small groups of cells located near the electrode recording tips 14. Because these cells are of different sizes and distances from the electrodes 12, 12', or 12", their action potentials will vary in shape and amplitude, and may be separated electronically or with computer software on the basis of these differences. FIG. 7(A) shows, for example, a hypothetical voltage recorded over time at one tip 14 of the multiwire bundle 10. The record shown in FIG. 9 can be seen to be composed of spikes of different amplitudes. At this stage, one of two major types of second stage processing of the recorded signals can be used.

The first type of processing is spike discrimination method known to persons skilled in the art. Still referring to FIG. 7(A), an example is shown in

an upper trace 60 where two distinct trains 61 and 62 of action potentials, from two different neurons or single "units" as they are often called by persons skilled in the field, are interleaved in the single electrode recording. The single unit spike trains 61 and 62 can be separated electronically on the basis of differences in their spike waveforms or amplitudes, and the discharge frequency of each neuron (frequency = 1/interval between spikes or action potentials). This separation yields two or more useful control signals, as shown in the lower traces 63 and 65 of FIG. 7(A), from a single electrode. Such spike train separation is, however, expensive in terms of needed hardware and software, thus raising the cost, bulk and complexity of any surgically implanted device. Moreover, single neurons may be damaged by small movements of the electrodes 12, 12', or 12", and their signals may be lost. Since the brain 1 can move slightly within the skull 2, particularly in relation to respiratory or cardiovascular induced changes in intracranial pressure, such relative movements can easily occur. Thus, while the spike discrimination method is one in current use today by many neurophysiological investigators, there have been as yet no published solutions to the problems of mechanical recording stability.

To circumvent the problems of mechanical recording stability, a new type of second-stage processing of recorded neural signals has been developed as demonstrated in FIG. 7(B). In this new method, the exposed surfaces of the recording electrode tips 14 are made slightly larger (400-1800 μm sq.) than is optimal for the isolation of single cell discharge, so that the spikes of several neurons are picked up simultaneously at each electrode tip 14. Furthermore, to reduce the possibility that the larger spikes of very nearby cells will dominate the record, only to be later lost through damage to the cells by the electrode 12, 12', or 12", the voltage signal is converted logarithmically. This conversion de-emphasizes the voltage contribution to the multi-unit record from nearby cells, and emphasizes that from the more numerous, more distant cells. The signal is then electrically rectified, yielding a signal 64 like that shown in the top trace of panel B. This trace 64 is actually the log rectified representation of the trace 60 in panel A. Thus, the

resulting signal S(t) 64 is given by: S(t) = log|V(t)|, where |V(t)| is the absolute value of the recorded multiunit voltage signal 60. Note that S(t) 64 is a positive function of both the log amplitude and the frequency of occurrence of the neural spikes. It is thus a measure of the density of neural activity in the vicinity of the electrode tip 14, a signal that tends to be more stable over time than the single unit method of recording described in the first method of processing neural signals.

Next, to convert this signal 64 to one that is more useful for control of some external device, S(t) 64 is integrated over a short time period to yield a signal 66 whose peak values correspond to the integral of activity over the preceding time interval (see FIG. 7(B)). A 33 msec integration interval is chosen because it is synchronized with the video recording frame duration, and it is found to be useful for experimental purposes. In practice, it should be a period of no longer than (l/2*f*), where *f* is the highest frequency component of the device movement speed that one wishes to generate. For human natural movement, *f* is on the order of 5 Hz. Thus, the integration period should not exceed (1/10) = 0.1 sec = 100 msec. At the end of each integration interval (33-100 msec), the peak value 67 of the integral 66 is then "read" by an electronic sample and hold (S-H) circuit, which is known to persons skilled in the art, the integrator is reset to zero, and another period of integration begins. The S-H circuit holds its value until the end of the next interval, and then jumps instantaneously to the new reading. Smoothing of the S-H output provides an analog signal 68 that is "smoother" than the original neural signal 60 yet still proportional to S(t) 64. Moreover, the analog signal 68 is much more useful for external device control because unwanted signals outside the frequency range of interest have been eliminated.

An example of the second stage of signal processing is shown in FIG. 8. During this stage of the processing, the recorded neural signals 60 having spikes are first converted logarithmically and rectified by the voltage converter 82 to yield a signal 64. Then, the signal 64 is integrated by an integrator 84 over a time period of no longer than (1/2*f*) to produce an integral 66, where the integrator 84 is connected to the voltage converter 82 as well

as a S-H circuit 86. The S-H circuit 86 receives the integral 66, reads the peak value of the integral 66, and provides an analog signal 68 after smoothing.

As an illustration, an example of these operations performed upon actual neural recordings from the brain of an alert monkey is shown in FIGS. 9(A) to (E). The trace in FIG. 9(A) shows the log amplitude of the multi-unit activity 160 recorded from a cluster of neurons in the sensorimotor cortex of the monkey, during flexion (161-163) of his elbow as shown in FIG. 9(E); note the increased activity during elbow flexion 162. The trace 164 in FIG. 9(B) shows the absolute or rectified value of the signal 160. The trace 166 as shown in FIG. 9(C) shows the output of the short interval, resettable integrator, and the trace 168 as shown in FIG. 9(D) shows the output of the S-H circuit that "reads" the value of the integrator at the end of each short integration period. The recordings are from experiments with a trained monkey, carried out during development of the technologies disclosed here. The time/voltage calibrations are 0.1 sec and 50 microvolts.

D. Third and Later Stages of Signal Processing

A summary of the third and subsequent stages of signal processing is shown in FIG. 10 according to a preferred embodiment of the present invention.

The processed signals 68 from the S-H circuit 86 are digitized by an analog/digital (A/D) signal converter 100 and then fed in parallel to (a) a multi-channel display system 102, and (2) a signal /movement cross correlation and distribution system 101. The display system 102 is an n-cell matrix, where "n" is an integer and each cell 104 in the matrix 102 represents a separate neural data channel. The system 102 provides a quick overview of the pattern of activity across the "n" selected neural recording channels for each of the integration periods described above, and is extremely useful for initially 'focusing in" on those channels that are most active during particular actual or attempted movement. The display system 102 includes a LED display, where the intensity of the LED lighting is a positive function of the

level of neural activity in that channel, or a small computer screen which displays the ongoing level of activity in each channel in the form of color-coded values. Typically, the range of neural activity is divided into eight levels for monitoring purposes, though it is actually digitized for subsequent processing with 12-bit accuracy.

The signal/movement cross correlation and distribution system 101 is preferably a "C" language software routine which performs the following operations as illustrated in FIG. 11 according to a preferred embodiment of the present invention:

(1) Determination of mean signal levels 112 on each channel when the subject is at "rest";

(2) Subtraction of the mean resting signal level 112 for each channel from the ongoing signal 110 of that channel, thus yielding a time-dependent signal D(t) 114 that departs from zero only when a movement is attempted;

(3) Computation of the cross correlations between D(t) 114 and the computerized display 116 of model arm (or joint) position, velocity, or acceleration (see the correlation table in step 2, FIG. 11) as observed by the subject during the calibration procedure described in detail below;

(4) On the basis of these correlations, selection of the channels 118 that will be most useful for control of movements or movement-related parameters of the external device;

(5) Routing/distribution of the selected channels 118 to the artificial neural nets (shown in FIG. 12) that will "shape" that signal for control of particular movements or of any other external device parameter.

Refer now back to FIG. 10. After selection of the subset 118 of channels that will be used to control a particular part of the external device, in this example movements about one of the "joints" in a robot arm, the signals on the channels 118 are fed to a three-layer, software or Artificial Neural Net (ANN) 103 for further processing, before passing to a peripheral device controller 107. After a succession of attempted or actual movements 105, in which each ANN 103 learns to "map" selected neural data channels 118 onto some measured output parameter, the ANNs 103 will thereafter shape the

input signals appropriately for device control. In the case of the paralyzed individual, the output parameter would be a desired or "calibrated" movement of the arm, or movement about a major joint in the arm, that (s)he observes on a computer display and "tries" to emulate with his/her own paralyzed arm. This "calibration" procedure is described in more detail in the next section.

The properties of a current ANN 103 used for this purpose are depicted in FIG. 12. The preprocessed neural signals 120, with resting back-ground levels removed, are fed from the particular neural channels 118 selected for control of wrist movements of a robot arm to each input node of a software ANN 103. The ANN 103 has a standard three layer, feedforward network that is trained using back propagation with momentum. The first layer contains three input nodes 122, the second, hidden layer contains five nodes 124, and the output layer has a single node 126 (scalar output). All of the nodes are fully interconnected in a strictly feedforward manner; i.e., each node in a layer is fully interconnected in a feedforward manner to every node in the next layer, and only to those in the next layer. For instance, each input node 122 receives input data 120 from all of the selected channels 118, it then sends an output to each node 124 in the middle or hidden layer. Each node 124 in the hidden layer receives inputs from each of the nodes 122 in the input layer. In turn, all nodes 124 in the hidden layer send outputs to the single node 126 in the final or ANN output layer. To further smooth out data transients that are outside of the control frequencies of interest (0-5 Hz), each data point fed to the ANN 103 comprises a running average of the current value of the neural signal in channel "m" (at time "t") plus the previous nine values of that signal (from time t-1 to t-9). This averaging period was determined by trial and error and may be changed to other values.

An example of the success of this three-layer net in mapping two channels of neural data onto a simultaneously obtained measure of an alert monkey's wrist position, according to a preferred embodiment of the present invention, is shown in FIGS. 13(A) and 13(B). Referring first to FIG. 13(A), top two traces 130 and 132 show processed multiunit activity (outputs of S-H circuits) from two channels, identified as channel 3 and channel 14

respectively, of a 36-electrode array implanted in the left motor cortex of a trained monkey, recorded as the animal flexed and extended his right wrist. Actual wrist position is shown by a third trace 134. Channel 3 shows a peak change in activity leading wrist extension, with a smaller elevation during wrist flexion. Channel 14 shows a large increase in activity leading and during wrist flexion, and a moderate increase during extension. Referring now to FIG. 13(B), output 138 of the ANN 103, which in this case is the position of the animal's wrist predicted from activity in neural channels 3 and 14, is shown by the heavy trace adjacent to an offset lighter movement trace 136 which shows his actual wrist position. Note the good correspondence, even though only two neural channels were used to compute predicted wrist position 138. The movement trace 136 is not the same as that shown in the previous trace 134, but was computed and recorded later, during training of the ANN 103. After the ANN 103 was trained over 10 movement trials, the match between actual and predicted wrist position attained a correlation of r = 0.96. Use of the ANN 103 output 138 to drive a robot "wrist" produced a robot wrist movement trace indistinguishable from the ANN 103 output 138.

Finally, referring back to FIG. 10, the output 138 of each neural net 103 is fed to an interface controller 107. An interface controller is a device which converts the output signals from one system into an appropriate set of signals for controlling some other system or device and known to persons skilled in the art. Interface controller 107 comprises a microprocessor which is programmed to convert the output of the neural net 103 into the voltages and currents that is necessary for actuating, for example, the robot controller, and thus moving the robot's wrist.

E. Calibration and Use of the System

FIG. 14 shows steps that are followed by a paralyzed individual in setting up, calibrating, and using a neurally control external device according to a preferred embodiment of the present invention. Here the control of an artificial limb, or of stimulation of paralyzed muscles of the limb, to produce a particular motion is used as a particular example. It is assumed in this

description that two prior conditions have been met. First, the electrodes have been implanted in brain regions that have been shown with functional imaging procedures to be under the subject's voluntary control; i.e., which are "activatable" by the subject when desired. If possible, they should also be implanted in a brain region that is normally activated when the subject attempts one or more of the particular movements that the prosthetic device will be asked to generate, though this is not an absolutely necessary requirement. Second, a prosthetic specialist will have already set channel gains and other parameters after device implantation. Each day or at selected intervals thereafter, the patient/subject would perform the following calibration routine.

First, (s)he learns to use a particular, monitored biological signal to turn on the system calibration computer when desired. If eye movements are intact, this signal could be a patterned sequence of eye blinks, sensed by a small monitoring device, that would not occur normally. If control of certain neck or facial muscles remains, their electromyographic activity could be used in the same coded way. In a totally paralyzed patient, the signal could be a particular time code of brain activity, generated voluntarily by the patient but unlike that which would occur during normal operation of the external device. A similar set of signals can be used for turning the calibration system off, or later, for turning the device to be controlled on or off when the neural control system has been calibrated.

Second, with the assistance of another person or again using a coded sequence of biological signals, the subject selects a particular movement for calibration from a predetermined list. The list may have the following options: alternate flexion and extension of the elbow; flexion-extension of the wrist; movements about the shoulder; grasping and releasing of an object; reaching to different points in space; or some combination of these.

When the subject gives a "ready" signal, the selected movement is displayed on a video monitor, simulated by animation or a video record of a model performing an actual movement. The model movement is performed at a slow to moderate speed and, during its performance, the subject "tracks"

the observed movement by attempting to move his/her own paralyzed limb in exactly the same manner and at the same speed. "N/2" repetitions would be performed, where N is a non-zero even integer. During these repetitions, the system (a) cross correlates the neural signals with the model movement(s) or some selected parameter (e.g., position, velocity, acceleration) of that movement; and (b) on the basis of the average of these correlations over the N/2 repetitions, determines which subset of neural channels was most highly correlated with the model movement and its parameters. The activity on the selected subset channels would then (c) be routed to the ANNs 103 which control the components of the external device that will produce a movement like the model movement. Another N/2 repetitions are then performed, and the appropriate ANNs 103 (d) "map" these selected neural inputs onto a stored record of parameter values for the model movement.

The subject now performs this same procedure for the next movement in the set, and the four steps (a) through (d) are repeated for that movement. And so on, until the entire calibration procedure has been performed. This procedure is performed daily or only at needed intervals (when the subject notices a diminution in control accuracy), with the optimal neural channels being re-selected at each calibration procedure and mapped again onto the desired movement functions. Thus, this periodic calibration procedure adapts to or allows compensation for changing neural signal parameters, and it ensures the optimal selection of those channels that are still useful at any time for device control.

Please note also that the subject's own brain can also adapt to changing signal properties and the challenges that these changes impose on device control. That is, if the subject can voluntarily activate the brain region from which signals are monitored and can vary these signal levels, then (s)he can learn to modulate these activation levels so that the external device can still be manipulated, even if there is drift or other unknown changes in the activity of the recorded neural channels.

Obviously, many modifications and variations of the present invention are possible to persons skilled in the art, without departing from the spirit and

the scope of the invention disclosed herein. It is to be understood, therefore, that the invention can be practiced otherwise than as specifically described.

CLAIMS

What is claimed is:

1. A device for collecting multicellular signals directly from a nervous system and transmitting the signals to an external receiver, comprising:

A) a plurality of electrodes formed in bundles of flexible wires with tips at staggered length aligned to be implanted in the nervous system for collecting multicellular signals; and

B) a signal processing mechanism connected to the electrodes for multiplexing and transmitting the signals from the electrodes to the external receiver.

2. The device according to claim 1, wherein the number of the flexible wires in a bundle ranges from 3 to 10.

3. The device according to claim 1, wherein the diameter of the flexible wires is smaller than 50 em.

4. The device according to claim 1, wherein the difference in length from one tip to its neighbor tip of the wires is variable.

5. The device according to claim 4, wherein the difference in length from one tip to its neighbor tip of the wires is about 0.3 to 0.6 mm.

6. The device according to claim 1, wherein the flexible wires in a bundle are made from noble metal.

7. The device according to claim 1, wherein the signal processing mechanism comprises:

A) an insulating substrate;

B) an array of electrode contact pads mounted on the substrate for receiving the electrodes, each electrode received individually by one of the electrode contact pads, and with the electrode contact pads being electrically isolated from each other at the substrate;

C) a microchip bonded in close contact with the substrate for receiving and multiplexing the signals from the electrodes; and

D) an electric connection to the microchip for relaying power to the microchip and transmitting the signals received at the microchip to the external receiver.

8. The device according to claim 7, wherein the electric connection is a hardware device.

9. The device according to claim 8, wherein the hardware device is a cable.

10. The device according to claim 7, wherein the electric connection is a wireless device.

11. The device according to claim 10, wherein the wireless device is a nonresonant wireless setup.

12. The device according to claim 11, wherein the nonresonant wireless setup comprises:

A) a first coil in connection with the microchip for relaying power to the microchip; and

B) a second coil in connection with the microchip for receiving and transmitting the multiplexed signals to the external receiver.

13. The device according to claim 10, wherein the wireless device is a resonant wireless setup.

14. The device according to claim 13, wherein the resonant wireless setup comprises:

A) a coil in connection with the microchip for relaying power to the microchip; and

B) a low pass filter in connection with the microchip for receiving and transmitting the multiplexed signals to the external receiver.

15. The device according to claim 7, wherein the microchip comprises signal processing integrated circuits.

16. An apparatus for recording multi-neuron signals directly from a nervous system comprising a plurality of sensors, wherein each sensor further comprises a bundle of noble metal wires with tips at staggered length.

17. An apparatus for recording multicellular signals directly from small clusters of neurons and broadcasting the signals to an external receiver, comprising:

A) an array of electrodes for receiving the signals;

B) a signal processor for multiplexing and transmitting the signals to the external receiver, wherein the signal processor comprises:

i) an insulating substrate;

ii) an array of electrode contact pads mounted on the substrate for receiving the electrodes, each electrode received individually by one of the electrode contact pads with the electrode contact pads being electrically isolated from each other at the substrate;

iii) a microchip bonded in close contact with the substrate for receiving and multiplexing the signals from the electrodes, wherein the microchip comprises signal processing integrated circuits; and

iv) a electric device connected to the microchip for relaying power to the microchip and carrying the signals from the microchip to the external receiver.

18. The apparatus according to claim 17, wherein the electrodes are formed in a bundle of noble metal wires with tips at staggered length.

19. The apparatus according to claim 17, wherein the electric device is a hardware connection.

20. The apparatus according to claim 19, wherein the hardware connection is a cable.

21. The apparatus according to claim 17, wherein the electric device is a wireless connection.

22. The apparatus according to claim 21, wherein the wireless connection is a nonresonant wireless setup.

23. The apparatus according to claim 22, wherein the nonresonant wireless setup comprises:

A) a first coil in connection with the microchip for relaying power to the microchip; and

B) a second coil in connection with the microchip for receiving and transmitting the multiplexed signals from the microchip to the external receiver.

24. The apparatus according to claim 21, wherein the wireless connection is a resonant wireless setup.

25. The apparatus according to claim 24, wherein the resonant wireless setup comprises:

A) a coil in connection with the microchip for relaying power to the microchip; and

B) a low pass filter in connection with the microchip for receiving and transmitting the multiplexed signals from the microchip to the external receiver.

26. An instrument for collecting multicellular signals directly from a nervous system and transmitting the signals to an external receiver, comprising:

A) at least one sensor for receiving the signals, wherein the sensor comprising:

i) a bundle of wires with staggered length in an array, wherein each wire has a tip for receiving the signals from the nervous system; and

ii) an optical cement bead through which the wires may pass for holding the wires in position in a selected distance from the most distant wire tip; and

B) a signal processor connected to the sensor for multiplexing and transmitting the signals from the sensor to the external receiver.

27. The instrument according to claim 26, wherein the selected distance is about 6-8 mm.

28. The instrument according to claim 26, wherein the wires are made from conductive materials.

29. The instrument according to claim 28, wherein the conductive materials are noble metal.

30. A method for using multicellular signals collected directly from a nervous system to control an external device comprising the steps of:

A) collecting multicellular signals directly from a nervous system;

B) multiplexing and broadcasting the signals to an external receiver;

C) receiving the signals for demultiplexing and separating the signals;

D) rectifying the signals; and

E) converting the signals logarithmically.

31. The method according to claim 30, further comprising the steps of:

F) integrating the log rectified signals over a short time period;

G) sample-hold reading of the peak value of the integral for generating a S-H output; and

H) using the S-H output for controlling the external device.

32. A channel display system for monitoring recorded multicellular signals, comprising:

A) a device for recording multichannel neural signals directly from a nervous system and broadcasting the signals;

B) an external receiver for receiving the signals;

C) electric connection means for connecting to an external receiver to relay the signals; and

D) a visual display for displaying the signals in a matrix, wherein each cell of the matrix represents a separate neural data channel.

33. The channel display system according to claim 32, wherein the visual display comprises an LED, wherein the intensity of illumination of the LED is a positive function of the level of neural signals fed from the related neural data channel.

34. The channel display system according to claim 32, wherein the visual display comprises a computer screen, wherein the color of each cell of the display matrix on the screen is coded according to the level of neural signals fed from the related neural data channel.

35. A method for using multicellular signals collected directly from a nervous system to control a prosthetic device comprising the steps of:

A) using a detective device with a plurality of electrodes to record multicellular signals directly from a nervous system;

B) multiplexing and broadcasting the signals to an external receiver;

C) processing the signals;

D) converting the signals in digital form; and

E) displaying the signals in a multi-channel visual display where the display in one channel correlates to signals collected from one electrode.

36. A method for using multicellular signals collected directly from a nervous system to control a device comprising the steps of:

A) setting up a calibration routine for a subject's learning of a movement;

B) developing a model for that movement;

C) using a detective device with a number of electrodes to record multicellular signals directly from the subject's nervous system, wherein one electrode represents one signal channel;

D) multiplexing and broadcasting the signals to an external receiver;

E) processing the signals;

F) converting the signals in digital form;

G) determining of mean signal levels over a period of 10 to 20 seconds for each channel where signals in one channel correlates to signals collected from one electrode when the subject is at rest;

H) subtracting the mean resting signal level for each channel from the signals recorded at different time to yield a signal as a function of time, D(t), that departs from zero only when a movement is attempted;

I) computing the cross correlation between D(t) and the computerized model of the attempted movement in terms of at least one motion parameter; and

J) selecting the neural channels which are useful for controlling the device or a component of the device based on the cross correlation calculation.

37. The method according to claim 36, further comprising the step of:

K) distributing the selected channels to neural nets for shaping the signals for control of the movement of the device.

38. The method according to claim 36, wherein the motion parameters are position, velocity, and acceleration.

39. An apparatus for collecting multicellular signals directly from a nervous system to control an external device, comprising:

A) sensors in an array for recording the signals;

B) a transmitter for broadcasting the signals;

C) a processor for receiving the signals, converting the signals logarithmically, and integrating the signals to generate a S-H output in analog form;

D) a converter for converting the signals in analog form into digitized signals;

E) a computing interface for performing neural signal/model movement cross correlation to select the signals that are most useful for control of a particular movement of the device and distributing the selected signals;

F) a microcomputer for supporting a feedforward neural network for receiving the selected signals and mapping the signals onto a model movement to generate control parameters; and

G) an interface controller for controlling the device to make movement same or similar to the model movement according to the control parameter.

40. A method for using a neural net to map neural signals onto desired movement or control parameters to control a device comprising the steps of:

A) recording neural signals in multichannels directly from a subject's nervous system;

B) removing resting background levels from the signals;

C) calculating a running average for each data point of the signals at time "t" in channel "m" by combining the previous several values of that signal;

D) feeding the signals from the particular channels selected according to the desired movement or control parameters in a feedforward direction to each input node of the neural net, wherein the neural net has at least three input nodes, and all the nodes are fully interconnected; and

F) outputting the signals from the neural net to a peripheral device controller.

41. A method for calibrating a neutral control system comprising the steps of:

A) turning on the control system;

B) selecting a model movement for calibration;

C) giving ready signal to the system;

D) displaying the selected model movement on a visual display;

E) allowing a subject to attempt to track or emulate the selected model movement;

F) recording neural signals from a number of neural channels of the subject during the attempted movement;

G) comparing the recorded neural signals with the selected model movement by correlation methods, so that the neural channels whose activity is most highly correlated with the attempted movement may be selected by the system;

H) repeating steps E) to G) for N/2 times, wherein N is a number equal to or greater than one; and

I) performing another N/2 repetitions of E) to G) to allow a neural net to map the recorded neural signals from the selected channels onto a set of parameters for the selected model movement.

42. A movement calibration system comprising:

A) a biological signal monitor for turning on or off the system;

B) a database for storing optimal parameters related to a family of model movements a subject attempts to make;

C) a visual display for displaying a movement selected from the database; and

D) a computer for matching the selected movement and the subject's attempted movements by calculating their correlation.

43. A method for using multicellular signals collected directly from a nervous system to control a prosthetic device comprising the steps of:

A) setting up a calibration routine for a subject's learning of a desired movement;

B) computerizing a "model" for that desired movement;

C) using a detective device with a number (n) of electrodes to record multicellular signals directly from the subject's nervous system when the subject attempts the desired movement, wherein each of the n electrodes represents one signal channel;

D) multiplexing and broadcasting the signals to an external receiver;

E) processing the signals for generating signals in analog form;

F) converting the signals into digital form;

G) determining of mean signal levels for each channel where signals in one channel correlates to signals collected from one electrode when the subject is at "rest";

H) subtracting the mean resting signal level for each channel as computed in step (G) from the collected ongoing signal to yield a signal as a function of time, D(t), that departs from zero only when a movement is attempted by the subject;

I) computing the cross correlation between D(t) and the computerized model of the desired movement in terms of kinetic parameters such as position, velocity, and/or acceleration;

J) selecting the neural channels which are most useful for controlling the device or a component of the device based on the cross correlation calculation; and

K) distributing of the selected channels to neural nets to shape the signals for controlling the device to produce a movement as same or similar to the desired movement.

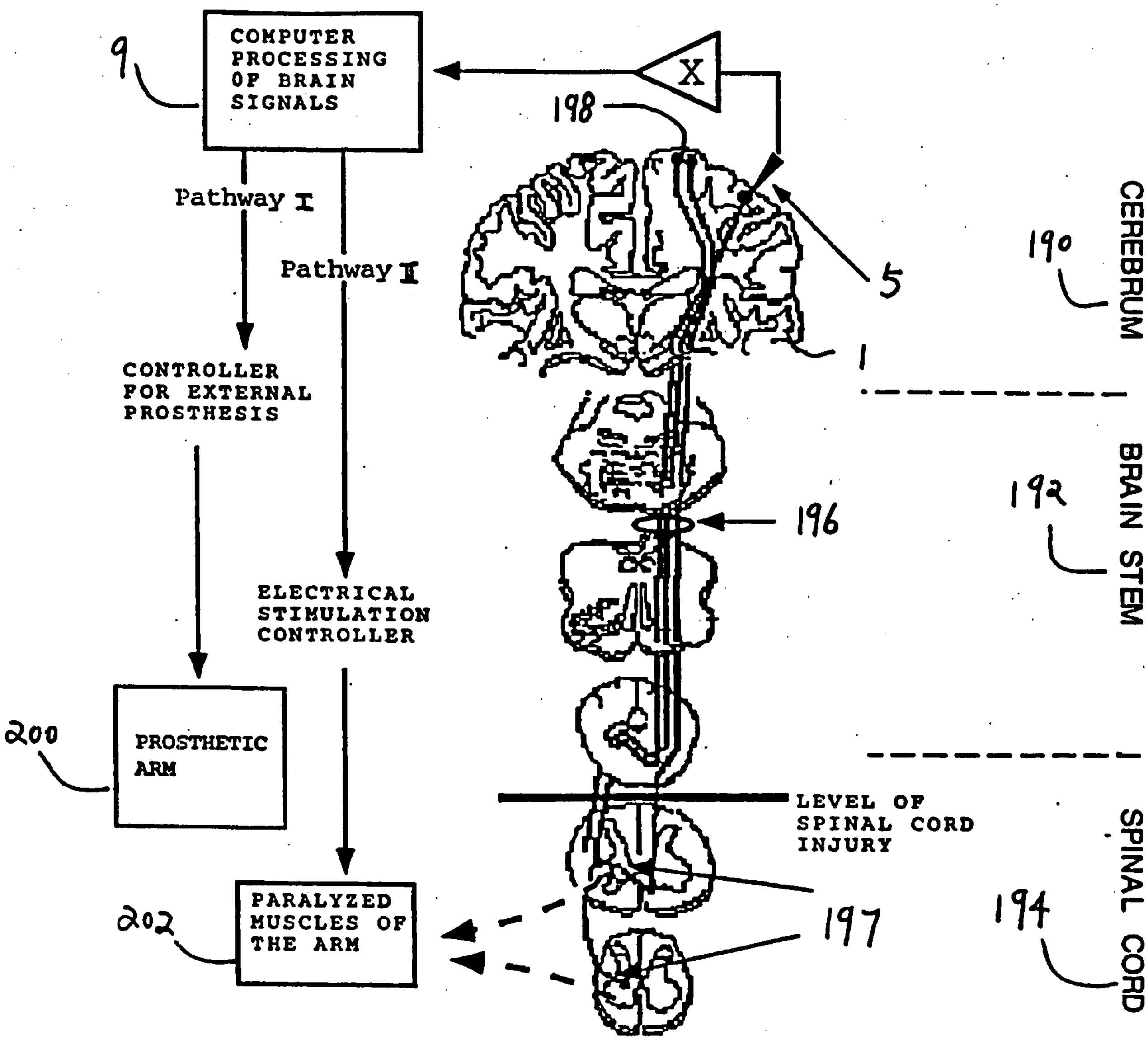

COMPUTER PROCESSING OF BRAIN SIGNALS
9
X
198
Pathway I
Pathway II
5
1
CEREBRUM
190
CONTROLLER FOR EXTERNAL PROSTHESIS
196
BRAIN STEM
192
ELECTRICAL STIMULATION CONTROLLER
200
PROSTHETIC ARM
LEVEL OF SPINAL CORD INJURY
SPINAL CORD
194
202
PARALYZED MUSCLES OF THE ARM
197

Fig. 1

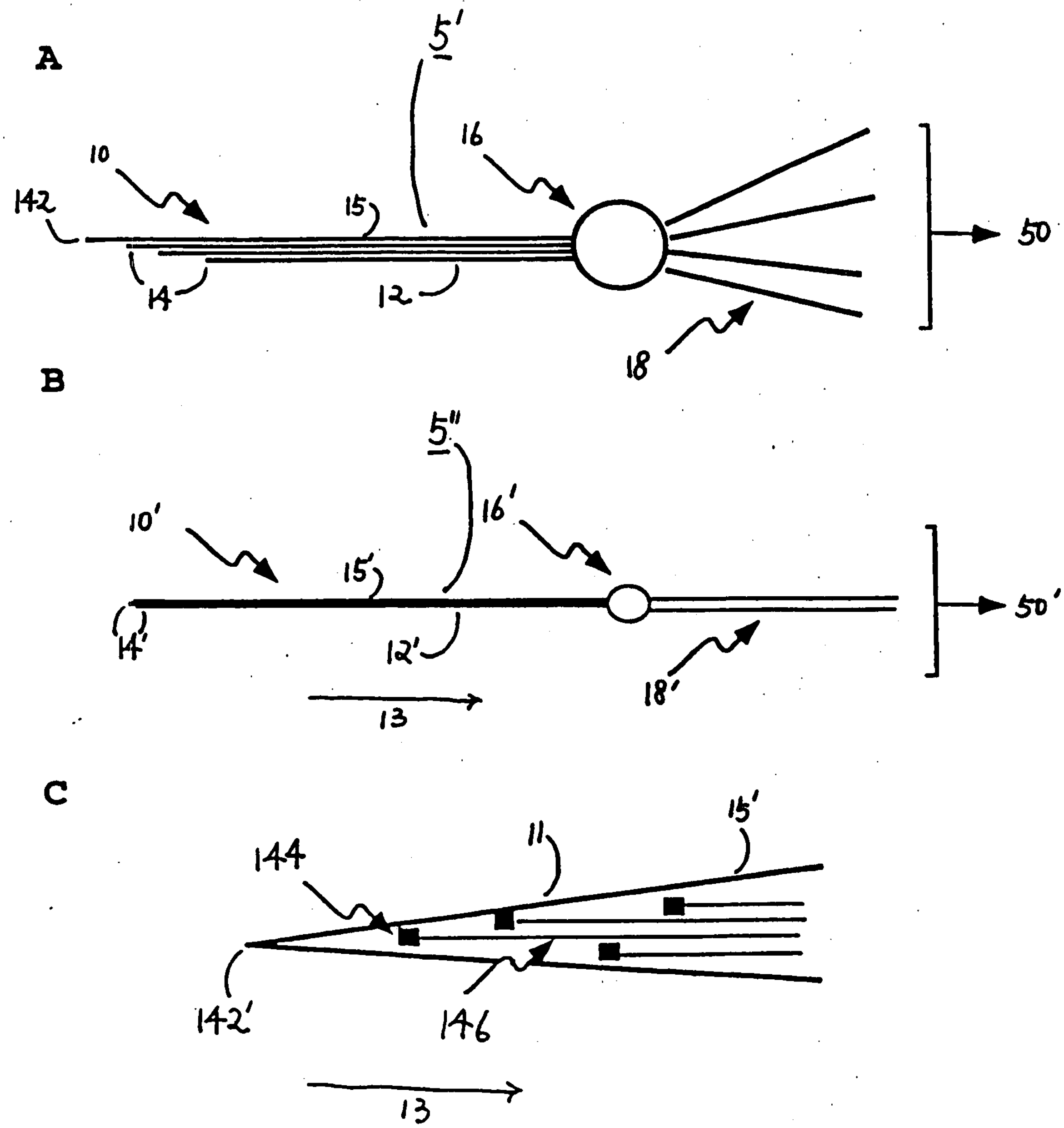

A
5'
10
16
142
15
14
12
50
18
B
5''
10'
16'
15'
14'
12'
18'
50'
13
C
15'
144
11
142'
146
13

Fig. 2

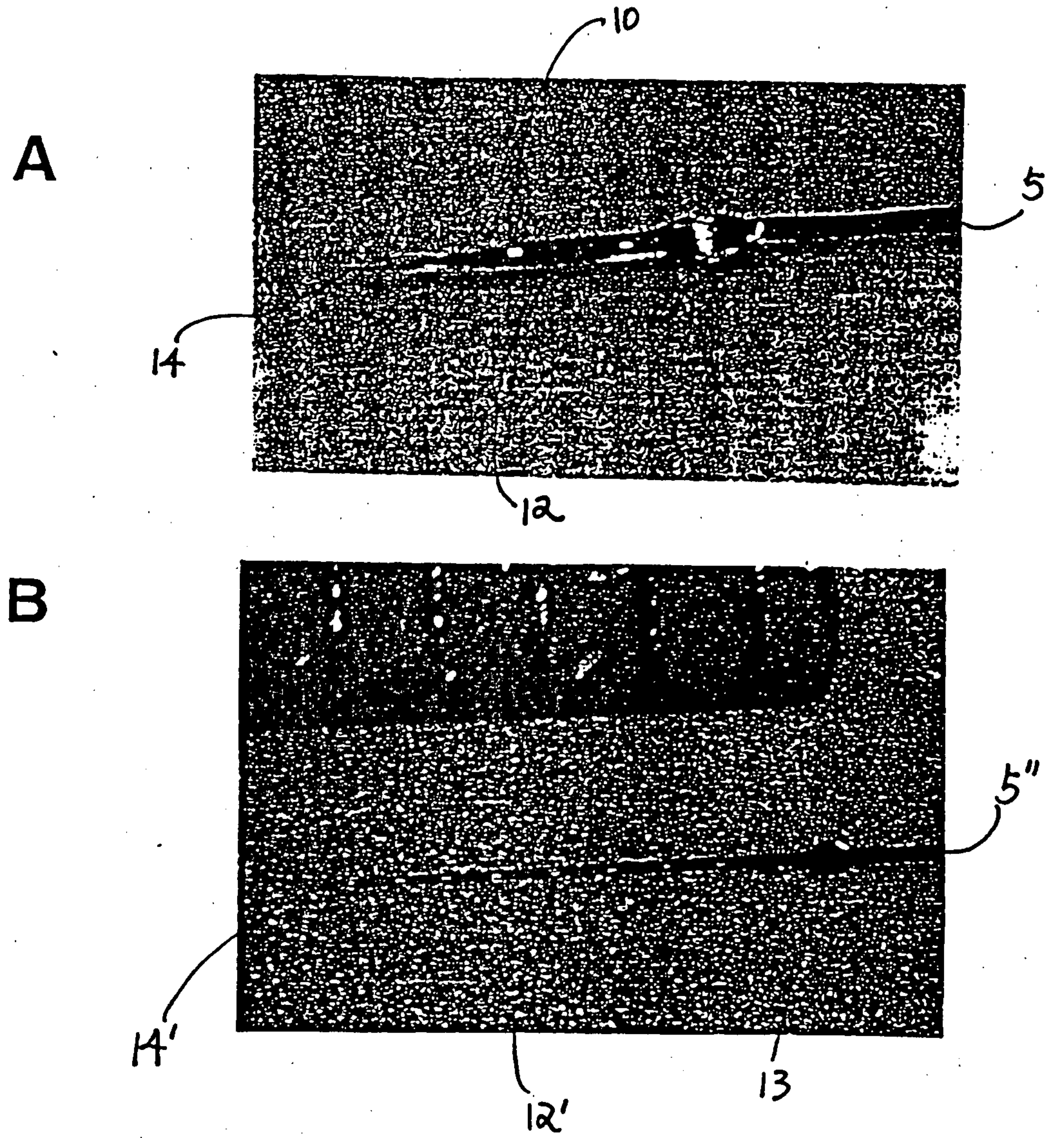


Fig. 3

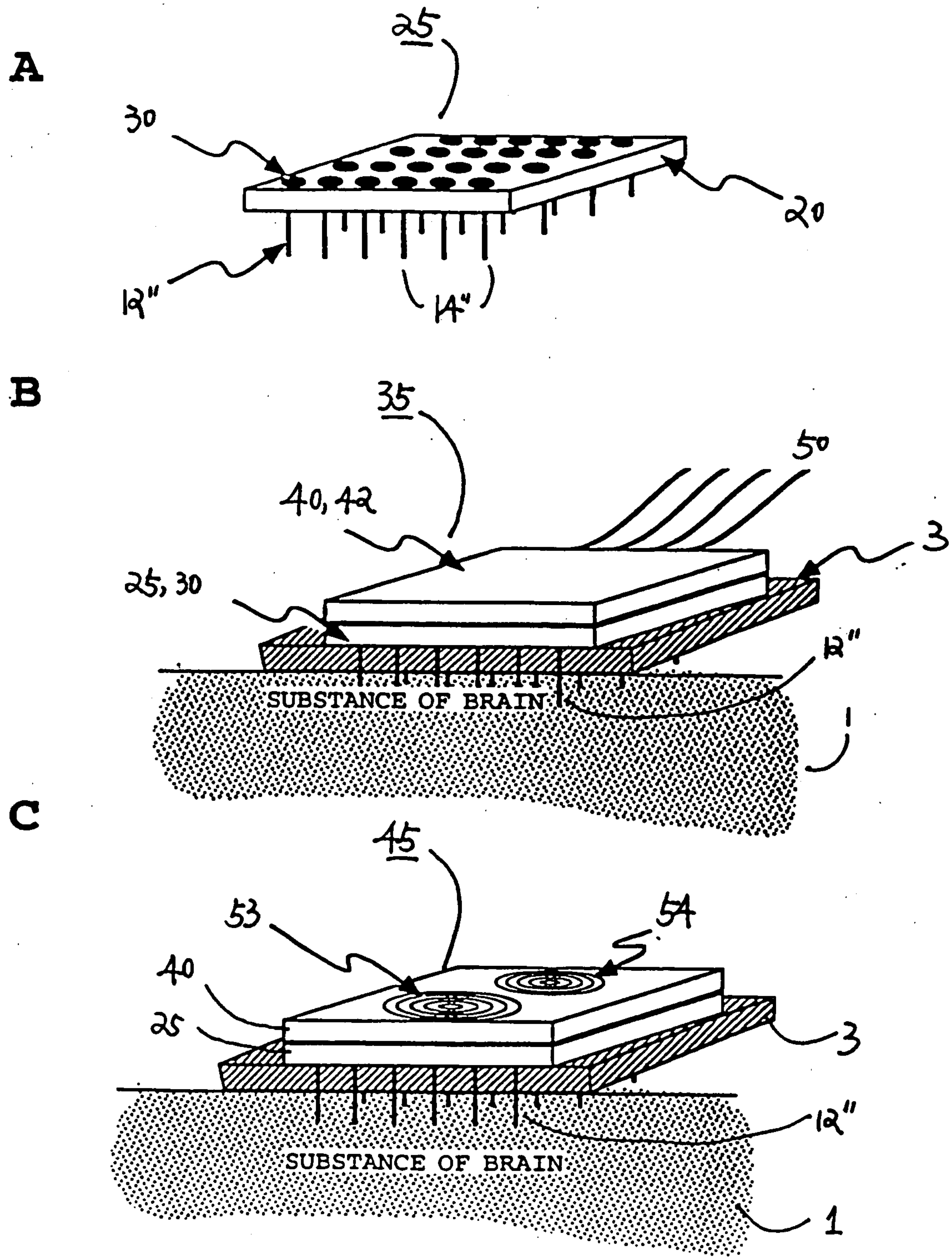

A
25
30
20
12"
14"
B
35
50
40, 42
3
25, 30
12"
SUBSTANCE OF BRAIN
1
C
45
53
54
40
25
3
12"
SUBSTANCE OF BRAIN
1

Fig. 4

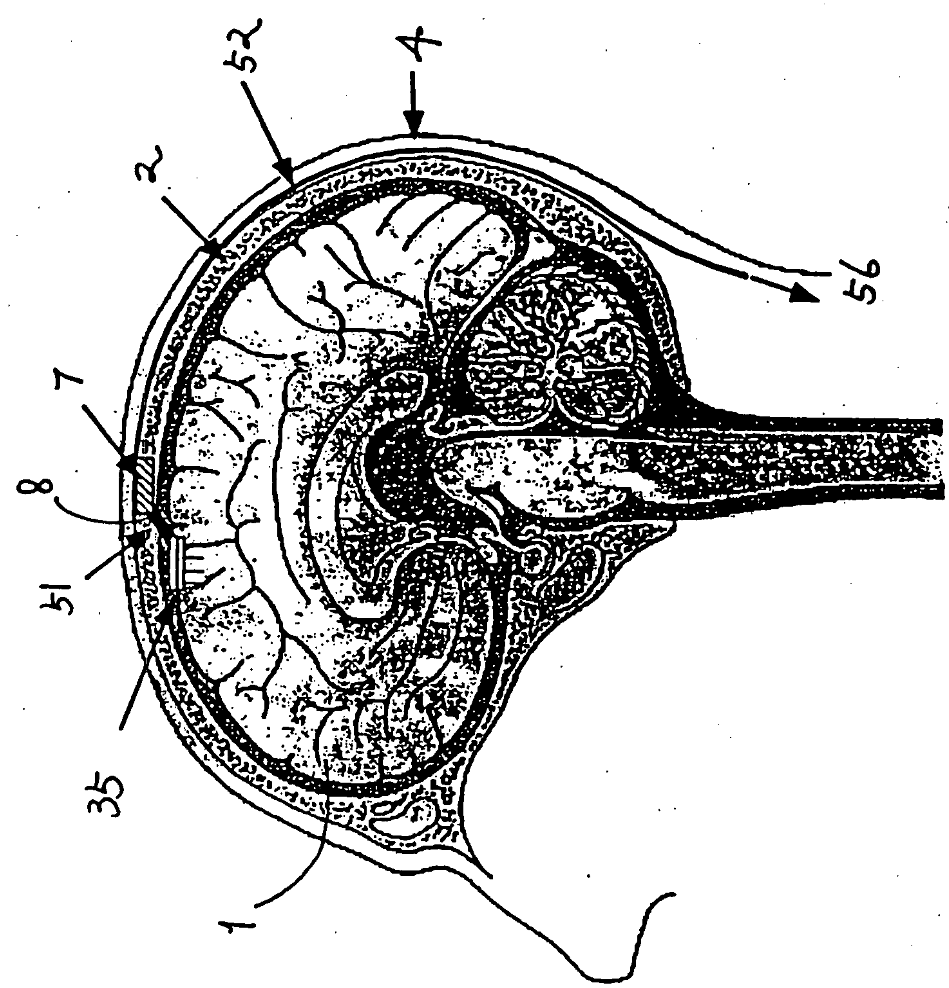


Fig. 5

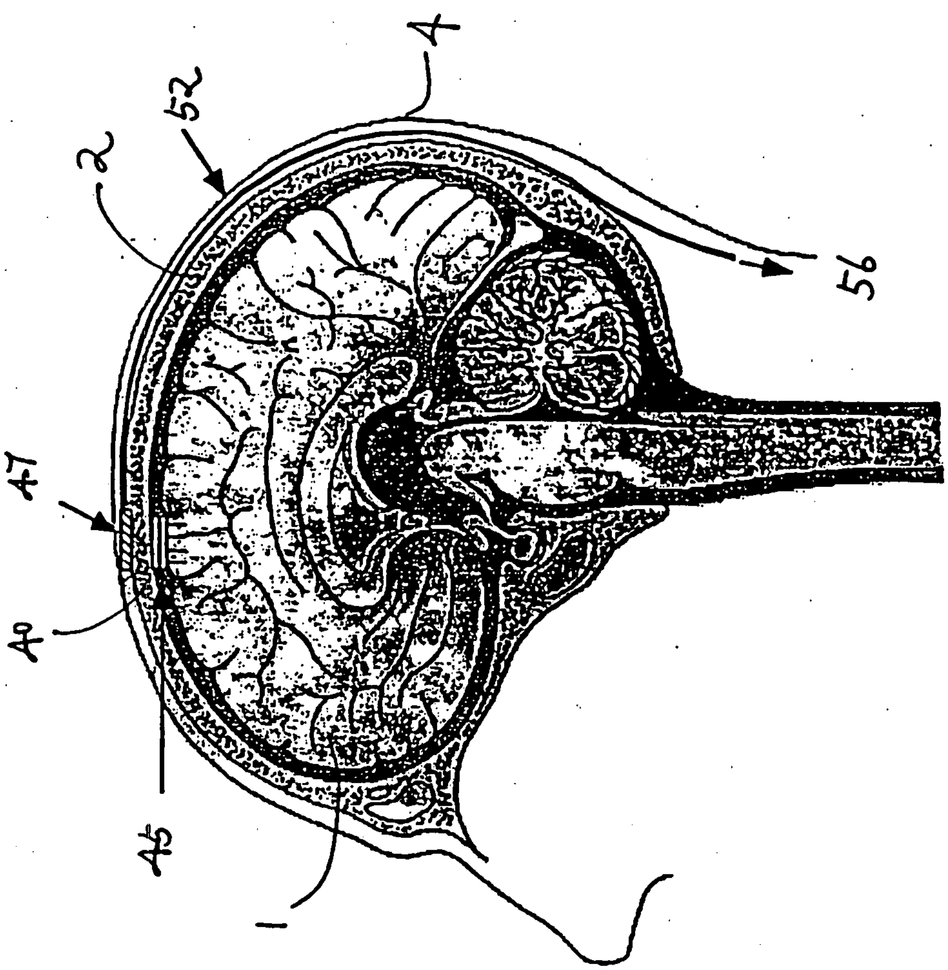


Fig. 6

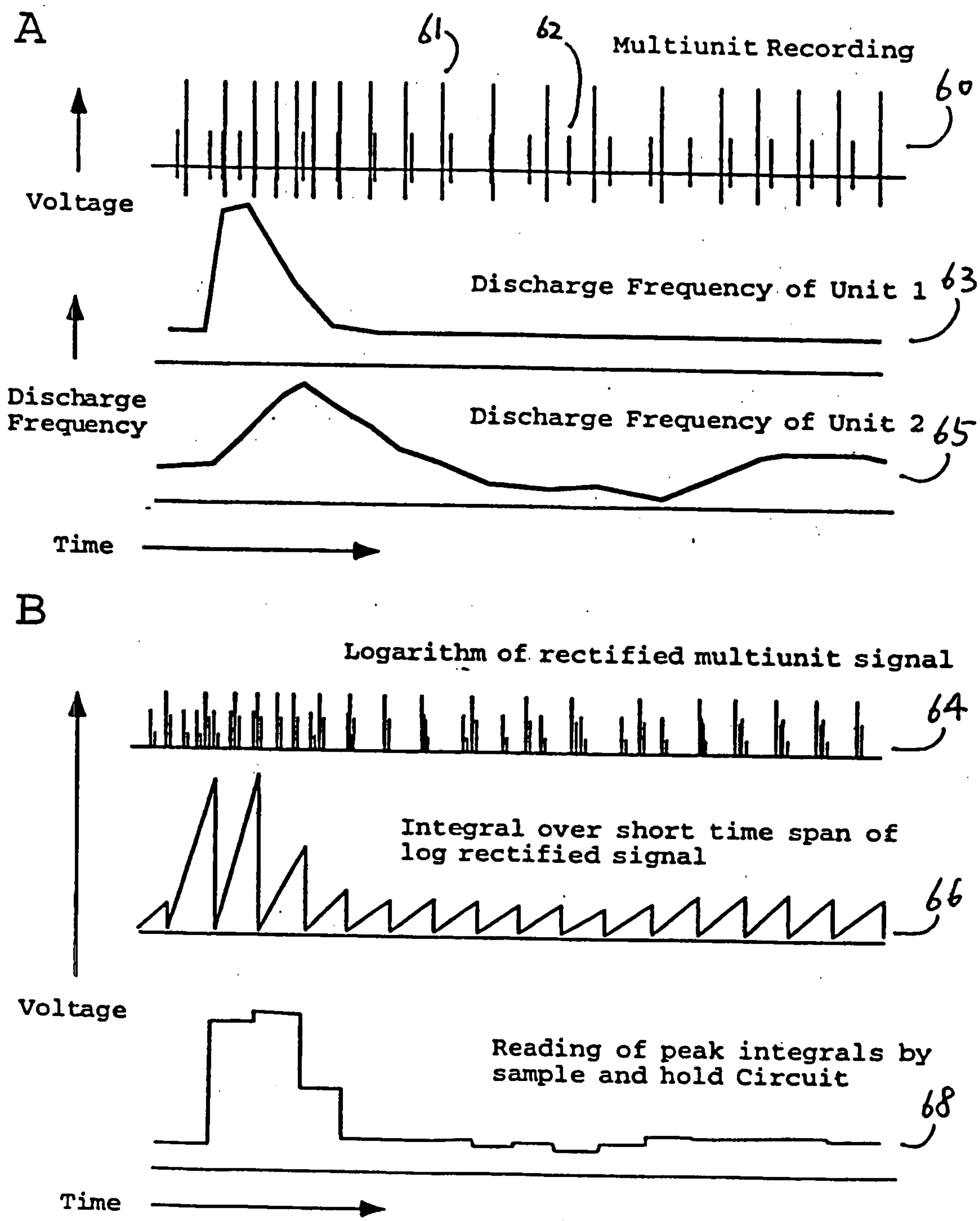

A
61
62
Multiunit Recording
60
Voltage
Discharge Frequency of Unit 1
63
Discharge Frequency
Discharge Frequency of Unit 2
65
Time
B
Logarithm of rectified multiunit signal
64
Integral over short time span of log rectified signal
66
Voltage
Reading of peak integrals by sample and hold Circuit
68
Time

Fig. 7

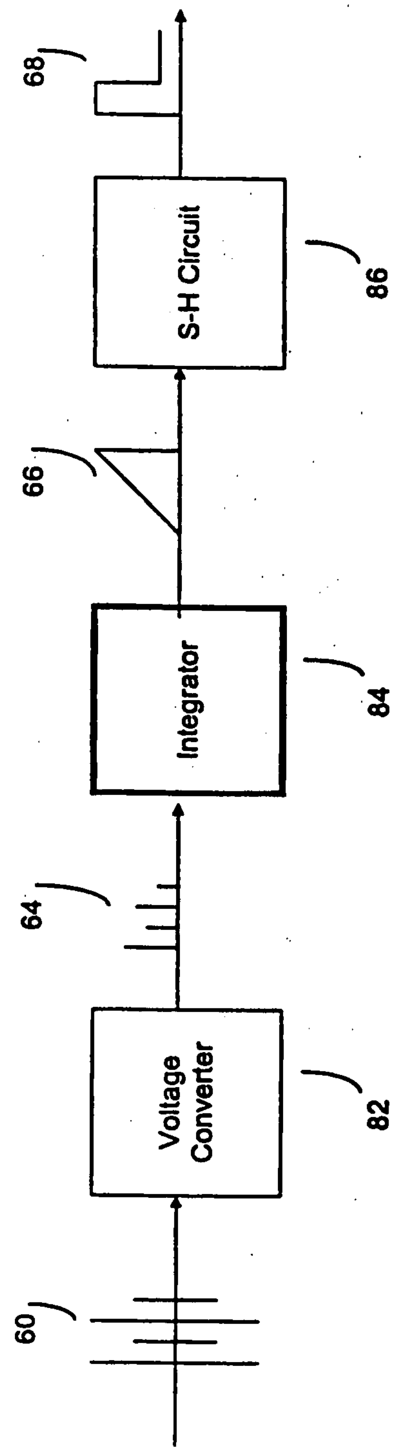


Fig. 8

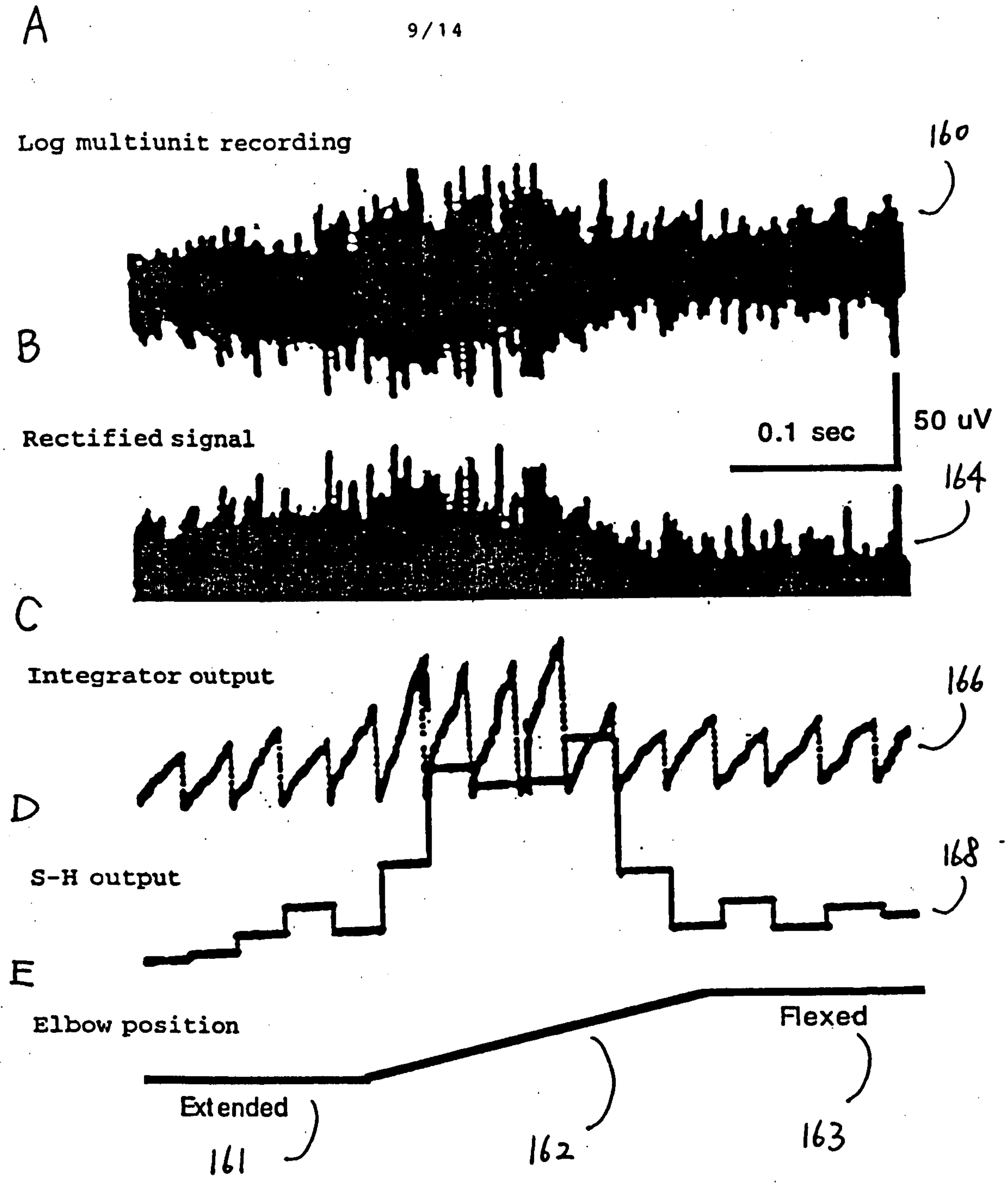

A
Log multiunit recording
160
B
Rectified signal
0.1 sec
50 uV
164
C
Integrator output
166
D
S-H output
168
E
Elbow position
Flexed
Extended
161
162
163

Fig. 9

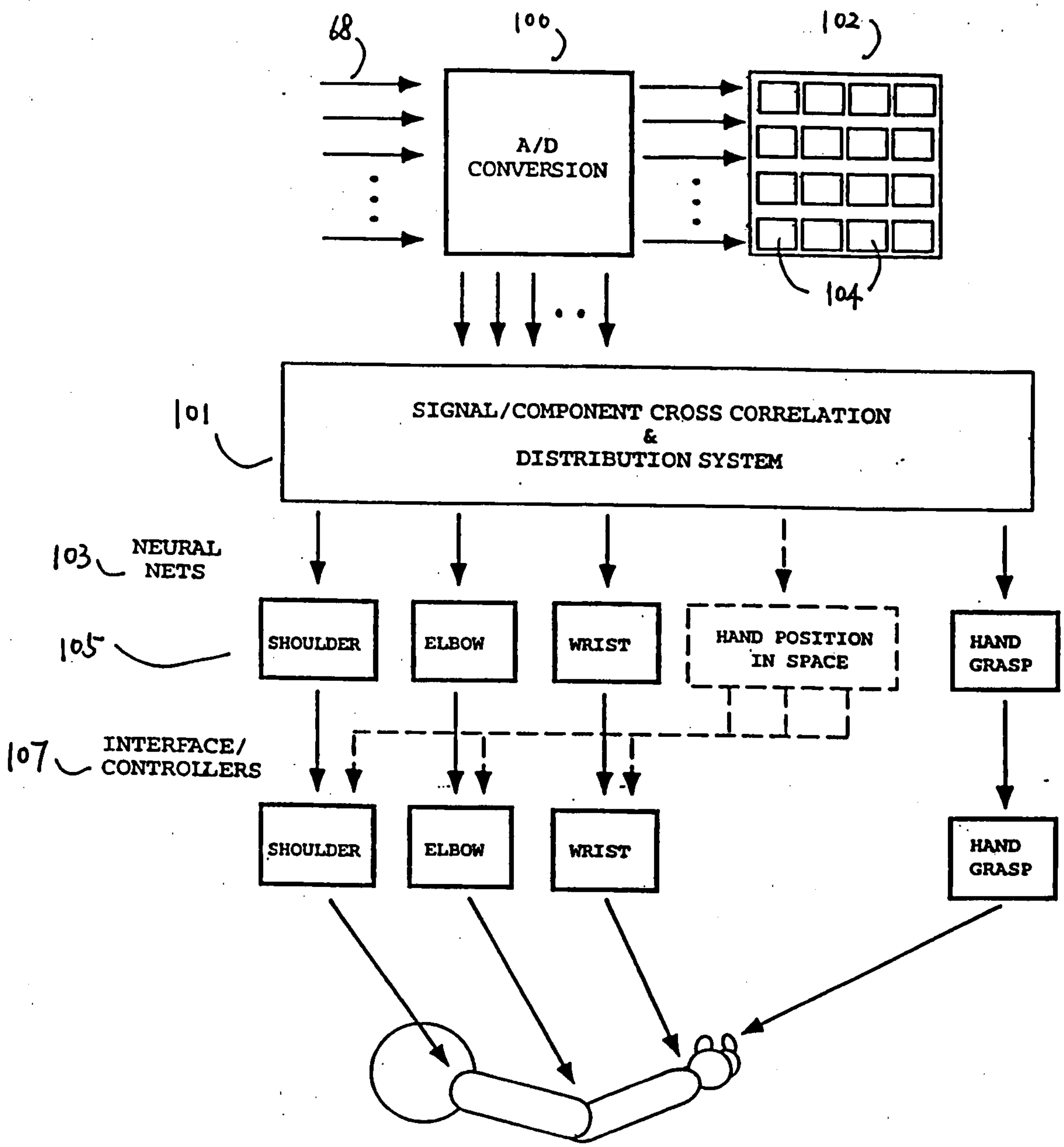
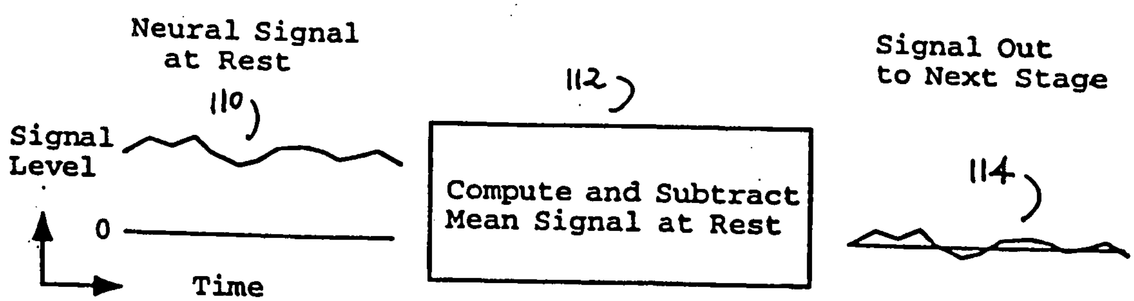

68
100
102
A/D
CONVERSION
104
101
SIGNAL/COMPONENT CROSS CORRELATION
&
DISTRIBUTION SYSTEM
103 NEURAL NETS
105
SHOULDER
ELBOW
WRIST
HAND POSITION IN SPACE
HAND GRASP
107 INTERFACE/ CONTROLLERS
SHOULDER
ELBOW
WRIST
HAND GRASP

Fig. 10

STEP 1



STEP 2

ATTEMPTED MOVEMENT 116

NEURAL CH	1	2	3	. .
1	0.8	0.2	-0.7	
2	-0.2	0.8	0.0	
3	0.7	0.4	0.5	
4	0.6	-0.3	0.9	
5	0.0	0.7	-0.1	
6	0.1	0.6	0.5	

MOVEMENT	CHANNELS SELECTED 118
1	1,3,4
2	2,5,6
3	1,4

Fig. 11

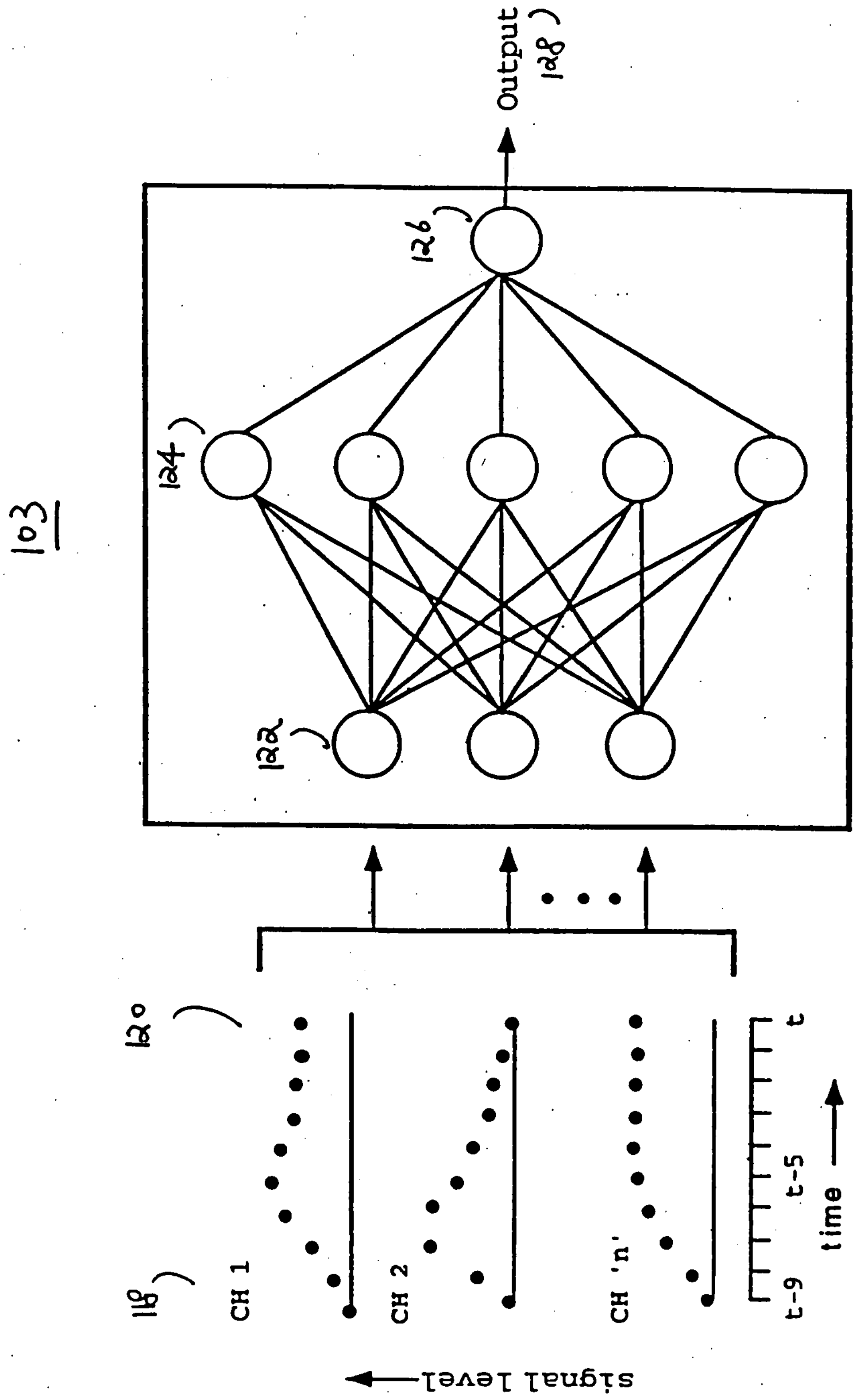

103
Output
128
126
124
122
120
118
CH 1
CH 2
CH 'n'
t-9
t-5
t
time
signal level

Fig. 12

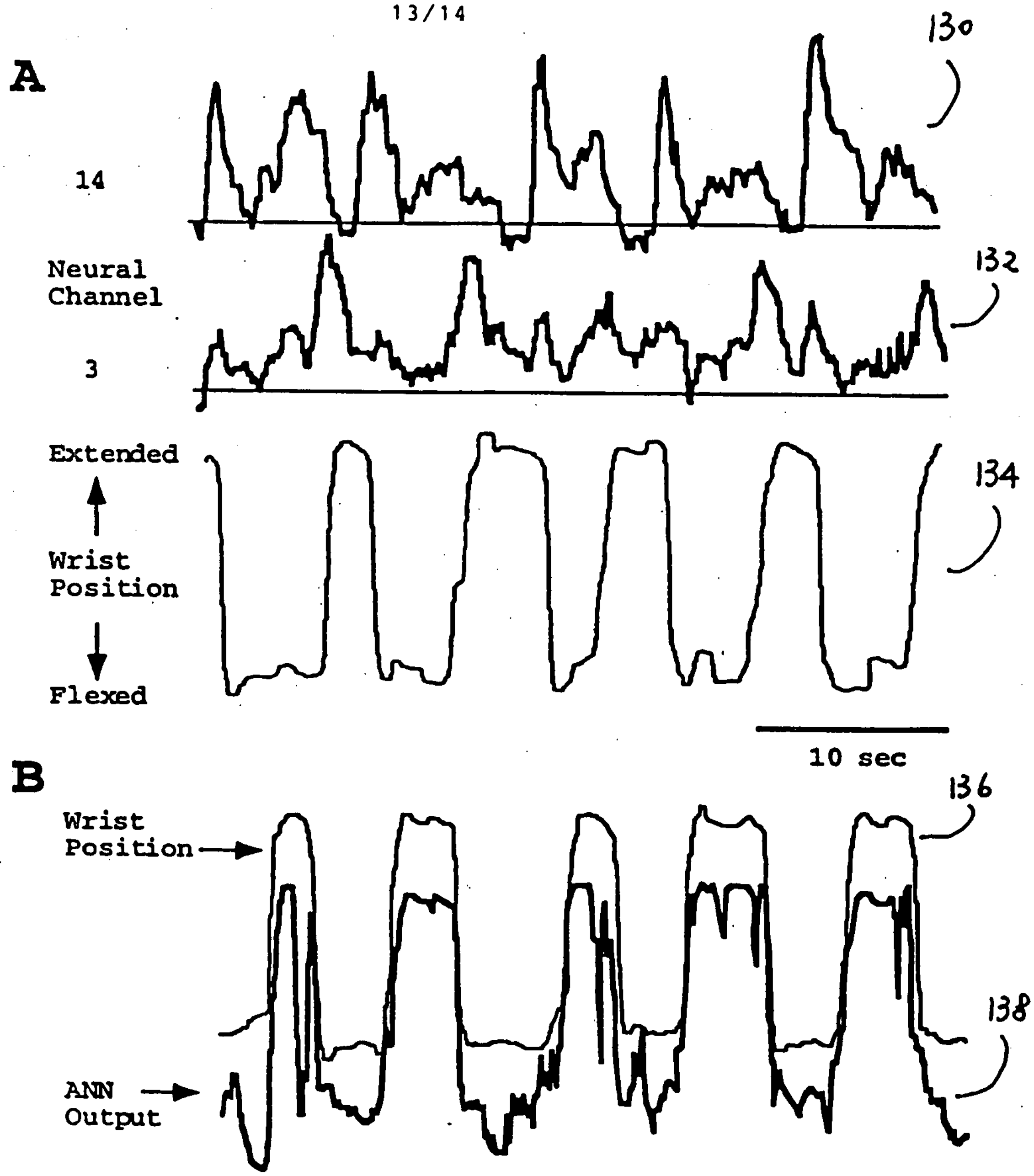
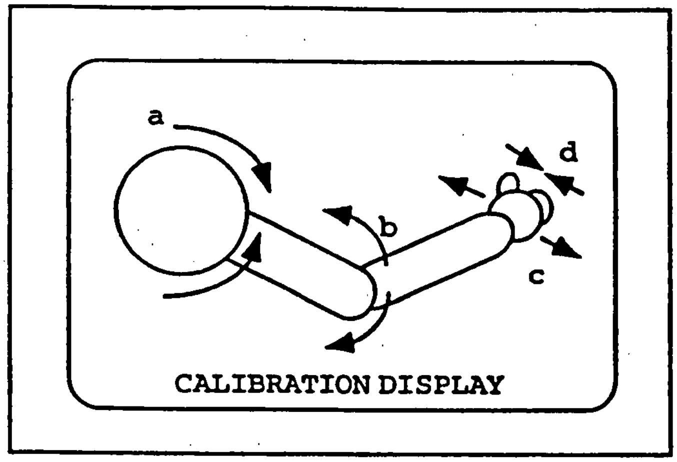

A
130
14
Neural
Channel
3
132
Extended
Wrist
Position
Flexed
134
10 sec
B
Wrist
Position
136
138
ANN
Output

Fig. 13

SYSTEM CALIBRATION METHOD



TURN ON CALIBRATION SYSTEM

SELECT MOVEMENT FOR CALIBRATION (a,b,..)

GIVE READY SIGNAL

ATTEMPT TO "TRACK" MOVEMENT

'N' MOVEMENTS ?

YES NO

LAST MOVEMENT TO BE CALIBRATED?

YES NO

NEXT MOVEMENT

END CALIBRATION

Fig. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18172

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/04
US CL :600/372, 378
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/372, 373, 377, 378, 383, 544, 546; 607/48, 49, 62, 116,-118; 606/130

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,178,161 A (KOVACS) 12 January 1993, entire document.	7-9, 15, 17, 19, 20, 35 --- 10-14, 16, 18, 21-25, 36, 37, 42
X --- Y	US 5,524,338 A (MARTYNIUK et al.) 11 June 1996, entire document.	1-6, 26, 28, 29 --- 16, 18, 27
X	US 5,413,103 A (ECKHORN) 09 May 1995, entire document.	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
05 NOVEMBER 1999

Date of mailing of the international search report
23 DEC 1999

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,279,305 A (ZIMMERMAN et al.) 18 January 1994, entire document.	10-14, 21-25
A	US 5,638,826 A (WOLPAW et al.) 17 June 1997, entire document.	1-43
A	US 5,215,088 A (NORMANN et al.) 01 June 1993, entire document.	1-43
A	US 5,692,517 A (JUNKER) 02 December 1997, entire document.	1-43

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/04

A1

(11) International Publication Number: WO 00/09008

(43) International Publication Date: 24 February 2000 (24.02.00)

(21) International Application Number: PCT/US99/18172

(22) International Filing Date: 11 August 1999 (11.08.99)

(30) Priority Data:
09/135,249 17 August 1998 (17.08.98) US

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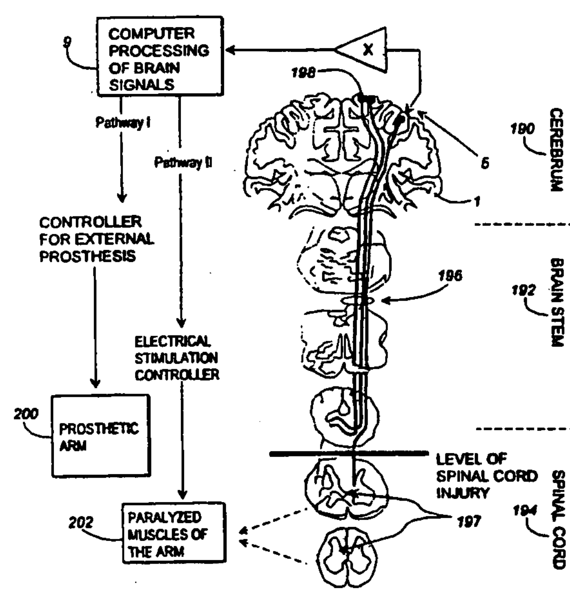
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYSTEM AND METHODS FOR CONTROLLING DEVICES BY BRAIN SIGNALS



(57) Abstract

A system and method control prostheses (200), other devices with signals received by sensors, implanted directly in the brain or other parts of the nervous system of a subject, and transmitted to an external receiver. Included in the system are sensors (5) in the form of bundles of small, insulated, flexible wires (10), configured in a parallel or twisted array, which are used to receive multicellular signals from small clusters of neurons. A new "calibration/adaptation" system is developed, in which the neural signals are cross–correlated with the parameters of a set of standardized or model movements as the subject/patient attempts to emulate the model movements, and on the basis of the correlations the neural signals that are best suited for control of the corresponding movement or movement parameter of the external devices are selected.

*(Referred to in PCT Gazette No. 46/2000, Section II)

SYSTEM AND METHODS FOR CONTROLLING DEVICES BY BRAIN SIGNALS

This invention relates generally to systems, methods and devices for interfacing between nerve cells (neurons) and external devices and, more particularly, to systems, methods and devices for extracting signals directly from the human brain and nervous system for use in the control of external devices.

BACKGROUND OF THE INVENTION

The human brain is an exceedingly complex processing system, which integrates continual streams of incoming sensory input data with stored memories, uses the input data and memories in complex decision processes at both conscious and unconscious levels, and on the basis of these processes generates observable behaviors by activation of its motor or movement control pathways and the muscles which these innervate.

In certain cases of traumatic injury or neurological disease, however, the brain is partially isolated from the periphery. Input data from certain senses are thus lost, at least for a portion of the body, as are many voluntary movements. Spinal cord injury is a well known example. With spinal cord injury, the pathways that link higher brain regions with the spinal cord and that are used for control of voluntary movements may be functionally transected at the site of injury. As a result, the patient is paralyzed, and (s)he can no longer voluntarily activate muscles that are innervated by regions of the spinal cord below the level of the injury. Despite the injury to their long fibers, however, many of the cells in these higher brain regions that control voluntary movement will survive and can still be activated voluntarily to generate electric signals for controlling voluntary movement. By recording directly from these cells with implantable devices (e.g., electrode arrays), signals generated by the cells may be "exteriorized" and used for the control

of external prostheses, such as an assist robot or an artificial arm, or functional electrical stimulation paralyzed muscles.

Another example of such loss occurs in cases of amyotrophic lateral sclerosis (Lou Gebrig's Disease), in which the motor neurons which control muscles, as well as some of the brain cells that control these motor neurons, degenerate. In advanced stages of this disease, the patient may have completely intact senses and thought processes, but is "locked in", so that neither movements nor behavioral expressions of any kind can be made. Providing these patients with some way of communicating with the external world would greatly enhance their quality of life.

In sum, there is a need to develop a system for monitoring and processing the electrical signals from neurons within the central nervous system, so that the brain's electrical activity may be "exteriorized" and used for the voluntary control of external prostheses or assist devices. In this way, damaged pathways are circumvented and some control of the environment can be restored. Because the electrical fields of small groups of neurons drop off rapidly with distance from the cells, this system should include surgically implanted "tiny" electrodes or sensors, which can be placed in close proximity to the cells that generate command signals for voluntary movement.

Earlier attempts to utilize signals recorded directly from neurons for the express purpose of controlling external prostheses have, however, encountered a number of technical difficulties. A major problem is how to obtain stable electrical signals of sufficient amplitude for real-time control of an external device. Two previous approaches have been used, but neither is successful in this regard.

In the first approach, microelectrodes with small tips (< 300 em sq. surface area) have been used, which are positioned to within 10-100 em of a single neuron, thus isolating its action potentials or "spikes" from that of other, more distant cells. In some cases, two or three adjacent neurons are recorded from simultaneously. In such cases, electronic devices are used to discriminate between the spikes of the individual cells and to sort their "spike

trains" into distinctly recognizable signals. One problem with this approach, however, is that the effective "isolation" of the spikes of only one to a few neurons requires that the recording electrode be positioned in close proximity to the neurons. Thus, to obtain such records from a sufficient number of movement-related brain cells, scores of electrodes should be implanted in the hope that a few of them will be in just the right position to record signals from one or only a few movement controlling cells. Given the required proximity of the electrode and the cells, there is a high probability, however, that small movements of the former with respect to the latter will result in signal loss either because the electrode moves slightly away from the cells of interest, or closer to them, resulting in cellular injury. With blood pressure induced pulsations of the brain within the skull, such relative movement is not only possible but very likely.

In recent years, small, multichannel, micromachined (integrated circuit) electrodes have been developed for use in neural recording. Given sufficient recording channel density, these electrodes promised a partial solution to the electrode/tissue movement problem described above. If the signal was lost from one channel by electrode movement, there was hope that it might be "picked" up by an adjacent channel, which moved closer to the active neuron at the same time that the previous one moved away. However, problems have been encountered with these electrodes as well. For reasons that are not entirely clear, neural signals are lost from these electrodes over time, due apparently to the formation of polarization potentials at dissimilar metal junctions along the recording channel, or the ensheathment and thus biological insulation of the electrode by glial cells.

A second approach is to use electrodes with larger exposed recording surfaces (in the range of 0.5 to 1.5 mm sq. surface area). These low impedance electrodes have lower noise characteristics than those with smaller tips, and can reliably record the activity of hundreds to thousands of neurons at greater distances than can the latter. Indeed, low level electroencephalographic (EEG) or field potentials can even be recorded from the surface of the scalp. This approach thus can avoid the difficulty of

different signal output levels caused by small movements between the electrodes and the selected cells encountered in the first approach. The use of the signals recorded in the second approach presents, however, a major problem for prosthesis control. In such recordings, the desired control signals may be of very low amplitude and may be "buried" within, or confounded by, EEG potentials from neurons that are not involved in voluntary motor processes. Thus, averaging must be used over many movement attempts to extract a usable signal. For this reason, this approach is less than desirable and perhaps not useful for real-time neural control of an external device.

Another problem, which occurs regardless of the electrode type used, is that neural signals may change over time for a variety of reasons: e.g., (a) naturally occurring cell death, which occurs randomly throughout the brain in adults; or (b) learning processes, which may, over time, alter the quantitative relationship between a neuron's activity and the external parts of the body to which it contributes voluntary control.

SUMMARY OF THE INVENTION

The present invention overcomes some of the difficulties described above with improved as well as new systems, methods and devices for obtaining signals directly from the brain or central nervous system, and for processing and utilizing these signals to control external devices. The systems described here are adaptable to a variety of signals from the brain or central nervous system as diverse as a) neurally generated electrical signals, recorded with microelectrode technologies from within the brain or with surface electrodes from extracranial sites; and/or (b) measures of localized blood flow that are correlated with neural activity, if techniques for miniaturization of current devices for making such measurements, in real time, are developed in the future. The external devices may include any device that can be controlled by processed electrical signals. These devices include, but are not limited to, artificial or prosthetic limbs; computer controlled. functional electrical stimulation of muscles of paralyzed individuals

for the restoration of movement; robots or robotics components; computers or computer displays; or the teleoperation of robots and machines in hostile environments.

A preferred embodiment of the invention represents a unique blend of technologies from the fields of neuro- or electro-physiology, biomaterials science, neural signal processing, functional brain imaging (to guide implantation of sensors), and robotics or prosthetics. Included in the embodiment is a unique recording arrangement with bundles of six to ten small (20-50 μm in diameter), insulated, and flexible, noble metal wires that are arranged in a parallel or twisted array. The wire bundles are constructed so that each recording wire can collect multicellular signals from a small cluster of neurons, with tips that are incremental in length, so that many recording sites can be sampled along a single line of bundle insertion into the brain.

According to another preferred embodiment, software routines, together with corresponding hardware, are used to perform specific signal correlation, adaptation, and distribution as part of a general recalibration procedure. A unique signal processing method is provided to convert recorded neural signals into a resultant signal that is useful for control of an external device. And, for the first time, the disclosed system incorporates neural net software routines to map actual neural signals onto desired movement functions.

In accordance with a preferred embodiment of the invention, a robot arm is controlled by the neural signals recorded directly from the voluntary movement (motor) control areas of the cerebral cortex of a subject, such as an alert monkey. It can be appreciated, however, that the concepts and general procedures of using neural signals to control movements of a robot arm, as described in the various preferred embodiments of this invention, are valid for the control of any external device that can be manipulated directly or indirectly by electrical signals and are not limited to use with monkeys or other trained animals. The followings are the devices and stages of signal processing system implementation in a particular preferred embodiment of the invention.

(1) Sensors (e.g., electrodes) and Sensor Arrays

Sensors and sensor arrays used in a preferred embodiment of the present invention should have appropriate geometry and size for the configuration of the neural implantation site, and the methods of construction of the wire bundles used in this embodiment allow such flexibility. In the present invention, these sensors are comprised of miniature, multichannel microelectrodes, either (a) fabricated with micromachining/photolithography methods, or (b) from noble metal (e.g., platinum or Pt) microwires, oriented along a single axis in a parallel or twisted array. For example, for extraction of signals from the "arm" control regions of the cerebral motor cortex of a human for the purpose of rudimentary control of a robot arm, an estimated minimum of 16-24 recording channels would be needed, with an electrode density of about 24/cm sq. Further, the implanted electrodes and arrays should be tailored to the required geometry of the implantation site, so that the electrode recording tips contact the correct cellular regions. The precise locations and shapes of the correct cellular regions can be determined prior to implantation by magnetic resonance imaging (MRI) and other brain imaging procedures. Multisite recording from cells with these regions is best accomplished by a wire bundle electrode array, with the recording tips of the bundled wires located at 0.5-0.6 mm intervals along the shaft of the array. When inserted normal to the cortical surface and aligned with cortical lamina V in the anterior bank of the central sulcus, this electrode array can sample activities from several clusters of the cortical output neurons that would normally control arm/hand movements. Because the wire bundle electrodes are made of a single noble metal, they do not suffer the loss of signals due to polarization potentials at dissimilar metal interfaces, as occurs in the micromachined electrodes constructed to date. Moreover, because the exposed (non-insulated) surface area of the wire electrode recording tip (400-1800 μm sq.) is larger than that typically used in an electrode designed for isolation of single neurons (150-300 μm sq.), signals can be recorded with the tips at a greater distance from the cells of interest, thus reducing the

probability of cellular injury by relative movements of the electrode with respect to brain tissue.

(2) Electronic Microchips

According to one aspect of the preferred embodiment, electronic microchips are needed for various purposes, such as amplification, filtering, multiplexing, and radio transmission of signals to external receivers. In the examples given below, preamplification of multiple channels of neural data, multiplexing of neural data from multiple channels into a single data stream, and radio transmission out of the body of a subject would be accomplished by chips coupled to the electrode array, that are on the order of 2 x 2 cm sq. or less in size.

(3) External Receivers and Demultiplexers

According to another aspect of the preferred embodiment, external receivers and demultiplexers are needed for allowing the exteriorized data stream to be detected and reseparated into separate neural data channels, which can then be individually selected and mathematically transformed for control of specific devices (e.g. an arm prosthesis) or device components (e.g., separate parts of the arm prosthesis).

(4) Signal Usage, Correlation, and Adaptation Methods

Once the neural signals are exteriorized, the most appropriate use for each should be determined. For example, if signals are derived from the "arm" area of the motor cortex, some of the signals are related to shoulder movements, others to movements about the elbow, some others to movements about the wrist, and the rest to finger movements. (In the paralyzed individual, of course, the movements are "attempted" rather than actual voluntary movements.) If the signals are not derived from the motor cortex but are still under voluntary control by the subject, and are to be used for control of arm prosthesis movements, a determination should also be made as to which are the most useful signals for fine hand control, which for upper arm control, and so forth.

Recorded neural signals may also change over time, due to electrode "drift" within the brain tissue (so that the electrode moves away from some

cells and closer to others), natural death of cells (50,000-100,000 cells/day in the adult brain), or changes in the parameters of cell discharge in relation to movement which result from motor learning. Consequently, a procedure according to the invention adapts to, or partially compensates for, changes in recorded neural signals and their parameters over time, so that the same implanted electrode array is useful for control purposes for as long as possible.

A general neural prosthesis calibration procedure, including newly conceptualized signal correlation, adaptation, and distribution (software) routines, accomplishes all of these goals. In this procedure, the subject observes a set of simulated arm movements (or other activities) on a computer screen, and attempts to "track" or emulate these same movements with attempted movements of his/her own (paralyzed) arm. During the emulation process, the activity on each neural channel is cross-correlated with selected parameters of the simulated motion (joint rotation, position of the hand in space, speed of movement, etc.), to determine with which it is most highly correlated. The activity of this most correlated channel is then "routed" or "distributed" to the circuit which controls the device component or movement parameter with which it is most highly correlated. Since this calibration procedure can be performed readily by the subject or patient on a periodic basis, the optimal neural channels for control of the external device can be reselected and redistributed each time, thus providing a continuing adaptation to changing neural signals, regardless of the cause of these changes.

(5) Shaping of Signals for Optimal Device Control

Once a subset of signals has been selected for control of an arm prosthesis (or other device), according to one aspect of the preferred embodiment, the signals should still be mathematically combined for optimal control of that device. For example, if neural signals "x and y" out of some larger set of signals correlate well with attempted hand movements about the wrist, and they are to be used for that purpose in controlling an arm prosthesis. they should still be mathematically processed to optimize such

control. By "optimal", it is meant that the processed signals should drive movements about the artificial wrist that match as closely as possible those model movements that are observed by the subject during the calibration procedure. To accomplish this, software networks are used for mapping actual neural signals onto desired movement functions; in the example referred to here, these would be the simulated arm/hand movements observed by the subject on the computer screen.

Accordingly, it is an object of the present invention to provide an improved system for recording neuronal signals directly from the brain or central nervous system for external device control.

It is another object of the present invention to develop an improved system which can be used with signals derived from small sets of selected single neurons, whose signals are separated from those of other nearby cells with electronic "spike" discrimination methods and are then recombined into a composite control signal.

It is a further object of the present invention to provide an improved system which can also be used with signals derived from small sets of neurons (2-10), whose signals are simply summed and electrically processed to obtain a useful signal for external device control.

It is yet another object of the present invention to provide multi-electrode sensors for recording from small clusters of neurons and providing signals that are midway between those obtained with the single neuron and EEG recording approaches described above.

It is yet a further object of the present invention to provide multichannel connectors and recording systems for use with the multi-electrode sensors.

It is also an object of the present invention to provide data reduction methods for converting the electrical activity signals recorded from clusters of neurons into useful intermediate control signals.

It is also another object of the present invention to provide an application of Neural Net algorithms for relating the intermediate control signals to movement parameters.

It is also a further object of the present invention to provide a novel calibration and adaptation method for periodically rematching recorded signals to the desired movements of an external device, so that compensation occurs for fluctuating signal amplitudes and/or motor learning.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and form a part of the specification, illustrate preferred embodiments of the present invention and, together with description, serve to explain the principles of the invention. In the drawings:

FIG. 1 is an exemplary diagram of a system according to the present invention for use by a subject with a spinal cord injury in voluntary controlling an external device.

FIGS. 2 (A) to (C) are schematics of sensors (electrodes) and sensor arrays according to the present invention for recording brain activity.

FIGS. 3 (A) and (B) are photomicrographs of recording arrays of the present invention used to monitor the activity of sets of cortical neurons.

FIGS. 4 (A) to (C) are diagrams of other embodiments of electrode arrays and methods for bringing power to and taking neural signals from an implantable microchip.

FIG. 5 is a diagram of an implanted device for externalizing neural signals for control of prosthetic devices.

FIG. 6 is a diagram of an implanted device according to a second embodiment for exteriorizing neural signals.

FIGS. 7 (A) and (B) are waveforms schematics of signals in the second stage of processing of recorded multiunit neural signals.

FIGS. 8 is a block diagram of a second stage of processing.

FIGS. 9 (A) to (E) are waveforms schematics of signals arising in the processing of multiunit recordings from the arm area of the sensorimotor cortex of a monkey.

FIG. 10 is a schematic of third and later stages of neural signal processing system, and an example of operation of the neural prosthesis for control of a prosthetic or a robot arm.

FIG. 11 is a diagram of operations performed by a movement calibration and signal distribution system depicted schematically in FIG. 10.

FIG. 12 is a schematic of an artificial neural net used to process neural input data before passing it to a peripheral device controller.

FIGS. 13 (A) and (B) are graphs showing examples of processed neural discharge and the real-time prediction of wrist position from this neural discharge by the artificial neural net of FIG. 12.

FIG. 14 is a flow chart showing steps used in calibrating the neural control system of FIG. 1, using as an example the control of an artificial limb or functional electrical stimulation of paralyzed muscles to produce a particular movement.

DETAILED DESCRIPTION OF THE DRAWINGS

Reference will now be made in detail to preferred embodiments of the invention, non-limiting examples of which are illustrated in the accompanying drawings.

A. Overview

With reference to FIG. 1, a system according to a preferred embodiment of the invention uses signals from cells in higher brain regions 1 can be activated voluntarily by a patient/subject, to in turn control external devices such as an artificial arm 200 and electrical stimulation of paralyzed muscles of an injured arm 202. FIG. 1 shows sections through various levels of the cerebrum 190, brain stem 192, and spinal cord 194. Also shown are pathways 196 that link the motor (movement control) areas of the cerebral cortex 198 with the spinal cord motor neurons 197 that control muscles of the arm 202. By recording directly from the cells in higher brain regions 1 with implantable devices 5 (e.g., electrode arrays), signals collected at the cells can, after processing by computer and electronic interfaces 9, be

"exteriorized" and used for the control of external prostheses, such as the artificial arm 200 (external pathway I) or the electrical stimulation of paralyzed muscles 202 (pathway II).

Alert monkeys that are trained to make specific arm movements in order to receive small food or juice rewards are used as subjects. Under surgical anesthesia and sterile conditions, arrays 5 of microelectrode sensors are implanted into the motor (voluntary movement control) areas of the animal's cerebral cortex 198, opposite the trained arm, preferably according to one of the methods as demonstrated in FIGS. 5-6. When the animal is fully recovered, signals from sets of neurons whose electrical activity is correlated in time with performance of these arm movements are identified, and the signals are processed mathematically for control of the robot arm as shown in FIGS. 7-11. This processing is such that the neural signals that are selected for control of a particular part of the arm (e.g., movements about the elbow) will, when applied to the controller for that part, produce robot arm movements that are very similar to those made by the animal. These "off-line" simulations allow of adjusting neural net parameters for optimal control of the robot arm as shown in FIG. 12. Again using positive reward procedures, the animals are then trained in 1 hour long daily sessions to adapt to the movements of the nearby robot arm, which their brain signals now begin to move roughly in parallel with their own arm movements. Delivery of the food rewards is then gradually made contingent not upon the accuracy of the animal's own arm movements, but upon those of the robot arm. Eventually, the animal's own movements can be temporarily restrained (by securing the sleeve of its training jacket), and he/she can obtain food solely through directly controlled movements of the robot arm with the neural signals recorded directly from his/her brain. The systems, methods, and devices according to various embodiments of the current invention can also be used by medical use with humans.

B. Sensors/Electrodes for Recording Neural Signals

Examples of the implantable devices 5 are shown in FIGS. 2 (A) to (C). FIG. 2(A) shows a preferred embodiment of sensors or a sensor array 5' according to the present invention for recording from cortical cells of a brain for extended periods of time. Six to ten small (25 to 50 μm diameter), insulated, noble metal, preferably Pt or Gold, wires 12 are bundled in a parallel or twisted array 10, with staggered length so that the exposed recording tips 14 end at different cortical depths (from the surface of the brain) when inserted into the brain.

In one embodiment of the invention, the wires 12 are constructed of 25 μm diameter Pt, insulated by a thin layer of Formvar, Isonel, or some other suitable material 15 obtained from the California Fine Wire Co. of Grover Beach, California. A completed wire bundle 10 made with 25 μm wire is approximately 75 μm in diameter. In another embodiment of the invention, the wires 12 are constructed of 50 μm diameter wire. A completed bundle 10 made with 50 μm diameter wire is about 150 μm in diameter, and is 15-35 mm long from electrode tip 14 to a connector assembly 50. Electrodes made with the 50 μm diameter wire isolate the electrical activities of small clusters of 3 or more neurons as well as those obtained with the 25 μm diameter wire.

The wires 12 are held in position with respect to one another by a light-cured optical cement bead 16, placed 6-8 mm from a most distant wire tip 142. The recording tips 14 of the individual wires 12 are located from 2 to 6-8 mm distal to the bead 16. The difference in length from one tip to its neighbor tip is substantially equal in one embodiment of the invention, about 0.5 to 0.6 mm, but these distances can be varied, depending upon the implantation site and its geometry. The bead 16, in one embodiment of the invention, is a small (0.5-0.6 mm diameter) drop of UV-curable acrylate, cured with 30 sec of UV exposure from a small, focused, UV gun. The cement bead 16 is also used for handling and manipulating the array 5' during its insertion into the brain, because of the bead's degree of rigidity. On the proximal side of the bead 16, the wires 18 separate to bundle loosely to the implanted connector

assembly 50 (see below). By inserting several staggered arrays 5' along the central sulcus of the cerebral cortex 198, where major motor areas exist, it is possible to place them all within the cortical layer that contains the corticospinal neurons that participate normally in the control of voluntary movement. MRI is used prior to surgery to locate this region precisely in relation to anatomical landmarks on the skull, thus guiding electrode implantation. Placement of eight to twenty of sensor arrays 5' in wire bundle form ensures recording from sufficient numbers of cells to capture a useful number of control signals.

An alternative type of sensor array 5" is shown in FIGS. 2(B) and 2(C), where the latter is an enlarged view of recording tips 14' shown in FIG. 2(B). In principle, the sensor array 5" is similar to the bundled wire array 5' shown in FIG. 2(A), except that in this case the entire array 5" is constructed by micromachining or photolithographic techniques. In the embodiment shown, each recording channel or "wire" 12' is a very thin (4-10 μm wide) strip of metal, left on a silicon substrate after etching away the surrounding metal. A long, sharp, insulating silicone substrate 11 contains six to eight separate recording channels 146, which end in uninsulated recording pads 144 at various sites along a sensor shank 13 which, when covered with a bead 16' of epoxy or similar material, can be used for gripping and manipulation (with fine tools) of the sensor array 5". Again, an enlarged bead 16' or disc region occurs along the shank 13. On the opposite side of this bead 16', separate (insulated) wire channels 18' course to a 1.0 mm diameter pad 50'. Though more desirable because of their small size and precise geometry, long-term recording was less successful with the micromachined sensor array 5" than with the sensor array 5' in wire bundles 10 described above and shown in FIG. 2(A). Reasons for this include micromachined sensor's greater fragility, difficulty in making connections with their channels, polarization potentials between their dissimilar metals which block electrode conductance, the encasement of the electrodes by glial cells, and insulating them from neural signals, when they are implanted.

Photomicrographs of the arrays 5' and 5" are shown in FIGS. 3 (A) and (B), respectively. FIG. 3(A) discloses a bundle 10 of pure platinum wires 12, insulated except at the tips 14. FIG. 3(B) shows a photo-lithographically prepared (micromachined) array 5". Thin, insulated conductors 12' travel from non-insulated recording pads 14' (just visible along the shank 13 of the electrode 5"), up a longer cable, and to a dispersed pad where electrical connections can be made.

FIGS. 4 (A) to (C) show yet other types of electrode arrays that may be used in the present invention. In FIG. 4(A), "n" parallel electrodes 12", each 2.5-3.0 mm in length, protrude from a silicone wafer 20 as an insulating substrate, each in electrical continuity with a gold contact pad 30 on the opposite surface of the wafer 20. The electrodes 12" are insulated except at the tips 14". Each of the electrodes 12" can be made from a short length of 90% Pt and 10% iridium wire or other noble alloy, which has sufficient stiffness over its short length to allow penetration of the pial covering of the brain and insertion into the cerebral cortex. An electrode array 25 of this type with each electrode 12" being a platinum plated silicon probe, but not in bundle form, is commercially available. As shown in FIGS. 4(B) and 4(C), an electrode array 25, as shown in FIG. 4(A), can be bonded to a second microchip 40 that contains "n" pads that mate precisely with those on the electrode array 25. The microchip 40 and the electrode array 25 are bonded in close contact and are then hermetically sealed. The microchip 40 may contain integrated circuits 42 that provide for amplification of the signals in each of the n electrodes or channels, and for multiplexing these signals into a serial data stream for transmission out of the brain 1. The microchip 40 and electrode array 25 set upon the meninges 3 (tissue coverings of the brain 1), but beneath the skull (not shown), and the electrodes 12" penetrate the meninges 3 into the substance of the brain 1 so that neural signals can be directly collected therefrom. The electrodes 12" which protrude from the array 25 may be individual wire leads, or short bundles of the type described above.

FIGS. 5 and 6 illustrate two possible ways that the signals may be led from the brain 1 to external processing units. The first is a communication channel established by a hardware connection as shown in FIG. 5, and the other is a communication channel established by a wireless mechanism as shown in FIG. 6.

Referring first to FIG. 5, in connection with FIG. 4(B), the implanted electrode array 35 has the first stage electronics circuitry 42 for signal processing (multichannel amplification and multiplexing) attached. Signals from the circuitry 42 are sent via a small, flexible cable 51 to a second stage device 7 implanted within the skull 2. An implant/skull junction 8 is hermetically sealed. This device 7 relays power from an implantable battery pack 56 connected to it by leads 52 beneath the skin and scalp 4. The implanted electronics 51, 7 and 42 are preferably programmable and contain circuitry for selecting (gating on) the neural channels to be used and for setting other recording parameters. They also preferably contain a transmitter for relaying the neural signals by RF signal to a receiver, which in turn relays it to demultiplexing and the later stages of neural signal processing described in more detail in the subsequent text and figures.

Referring now to FIG. 6, in connection with FIG. 4(C), there is shown an alternative implant method, according to a preferred embodiment of the invention, which uses a wireless mechanism, thereby allowing the cranium (skull) 2 to be reclosed, and thus reducing chances of infection. The electrode implant array 45 contains the microchip 40 which has multichannel amplifiers, multiplexing circuitry, and an RF transmitter. Attached to the microchip 40 are two coils 53 and 54 (as shown in FIG. 4(C)). One coil 53 allows power to be transmitted to the implant array 45 via a coil in an external unit 47 by induction, and the second coil 54 allows transmission of the multiplexed, multichannel neural signal out as a serial data stream. The external unit 47 contains a power coil, and a chip for conversion of DC voltages into the AC voltages that are necessary for inductive coupling to the internal coil 53. All devices are implanted beneath the skin. Battery packs 56 and the external unit 47 can be changed by simple surgical procedures if

necessary. With the technique shown in FIG. 6, the skull 2 is closed completely. While coils are used to describe the way that signals are led from the brain to external processing units by a nonresonant wireless mechanism, other kinds of devices, such as LC circuits or low pass filters, can be utilized to establish a resonant wireless mechanism to relay the signals as well.

Both techniques shown in FIGS. 5 and 6 allow for complete implantation of the first stages of the system. In the first method (FIGS. 5 and 4(B)), a junction 8 is hermetically sealed between the cranial implant site 51 and the second stage device 7. In the second method (FIGS. 6 and 4(C)), the skull 2 is resealed completely. In both cases, surgical removal and updating or replacement of implant components is possible if necessary.

When these electrode arrays and devices are to be implanted in humans, functional MRI (fMRI) technology may first be used to identify those brain regions that the patient still has under voluntary control, thus allowing precise, functional placement of the implants and the recording electrodes.

C. Second Stage Processing of Neural Signals

The types of neural signals recorded with the electrode technologies described above are shown schematically in FIGS. 7(A) and (B). Typically, the recorded neural signals include action potentials or "spikes" (brief, voltage transients) which signal the discharge of small groups of cells located near the electrode recording tips 14. Because these cells are of different sizes and distances from the electrodes 12, 12', or 12", their action potentials will vary in shape and amplitude, and may be separated electronically or with computer software on the basis of these differences. FIG. 7(A) shows, for example, a hypothetical voltage recorded over time at one tip 14 of the multiwire bundle 10. The record shown in FIG. 9 can be seen to be composed of spikes of different amplitudes. At this stage, one of two major types of second stage processing of the recorded signals can be used.

The first type of processing is spike discrimination method known to persons skilled in the art. Still referring to FIG. 7(A), an example is shown in

an upper trace 60 where two distinct trains 61 and 62 of action potentials, from two different neurons or single "units" as they are often called by persons skilled in the field, are interleaved in the single electrode recording. The single unit spike trains 61 and 62 can be separated electronically on the basis of differences in their spike waveforms or amplitudes, and the discharge frequency of each neuron (frequency = 1/interval between spikes or action potentials). This separation yields two or more useful control signals, as shown in the lower traces 63 and 65 of FIG. 7(A), from a single electrode. Such spike train separation is, however, expensive in terms of needed hardware and software, thus raising the cost, bulk and complexity of any surgically implanted device. Moreover, single neurons may be damaged by small movements of the electrodes 12, 12', or 12", and their signals may be lost. Since the brain 1 can move slightly within the skull 2, particularly in relation to respiratory or cardiovascular induced changes in intracranial pressure, such relative movements can easily occur. Thus, while the spike discrimination method is one in current use today by many neurophysiological investigators, there have been as yet no published solutions to the problems of mechanical recording stability.

To circumvent the problems of mechanical recording stability, a new type of second-stage processing of recorded neural signals has been developed as demonstrated in FIG. 7(B). In this new method, the exposed surfaces of the recording electrode tips 14 are made slightly larger (400-1800 μm sq.) than is optimal for the isolation of single cell discharge, so that the spikes of several neurons are picked up simultaneously at each electrode tip 14. Furthermore, to reduce the possibility that the larger spikes of very nearby cells will dominate the record, only to be later lost through damage to the cells by the electrode 12, 12', or 12", the voltage signal is converted logarithmically. This conversion de-emphasizes the voltage contribution to the multi-unit record from nearby cells, and emphasizes that from the more numerous, more distant cells. The signal is then electrically rectified, yielding a signal 64 like that shown in the top trace of panel B. This trace 64 is actually the log rectified representation of the trace 60 in panel A. Thus, the

resulting signal S(t) 64 is given by: S(t) = log|V(t)|, where |V(t)| is the absolute value of the recorded multiunit voltage signal 60. Note that S(t) 64 is a positive function of both the log amplitude and the frequency of occurrence of the neural spikes. It is thus a measure of the density of neural activity in the vicinity of the electrode tip 14, a signal that tends to be more stable over time than the single unit method of recording described in the first method of processing neural signals.

Next, to convert this signal 64 to one that is more useful for control of some external device, S(t) 64 is integrated over a short time period to yield a signal 66 whose peak values correspond to the integral of activity over the preceding time interval (see FIG. 7(B)). A 33 msec integration interval is chosen because it is synchronized with the video recording frame duration, and it is found to be useful for experimental purposes. In practice, it should be a period of no longer than ($l/2f$), where f is the highest frequency component of the device movement speed that one wishes to generate. For human natural movement, f is on the order of 5 Hz. Thus, the integration period should not exceed (1/10) = 0.1 sec = 100 msec. At the end of each integration interval (33-100 msec), the peak value 67 of the integral 66 is then "read" by an electronic sample and hold (S-H) circuit, which is known to persons skilled in the art, the integrator is reset to zero, and another period of integration begins. The S-H circuit holds its value until the end of the next interval, and then jumps instantaneously to the new reading. Smoothing of the S-H output provides an analog signal 68 that is "smoother" than the original neural signal 60 yet still proportional to S(t) 64. Moreover, the analog signal 68 is much more useful for external device control because unwanted signals outside the frequency range of interest have been eliminated.

An example of the second stage of signal processing is shown in FIG. 8. During this stage of the processing, the recorded neural signals 60 having spikes are first converted logarithmically and rectified by the voltage converter 82 to yield a signal 64. Then, the signal 64 is integrated by an integrator 84 over a time period of no longer than ($1/2f$) to produce an integral 66, where the integrator 84 is connected to the voltage converter 82 as well

as a S-H circuit 86. The S-H circuit 86 receives the integral 66, reads the peak value of the integral 66, and provides an analog signal 68 after smoothing.

As an illustration, an example of these operations performed upon actual neural recordings from the brain of an alert monkey is shown in FIGS. 9(A) to (E). The trace in FIG. 9(A) shows the log amplitude of the multi-unit activity 160 recorded from a cluster of neurons in the sensorimotor cortex of the monkey, during flexion (161-163) of his elbow as shown in FIG. 9(E); note the increased activity during elbow flexion 162. The trace 164 in FIG. 9(B) shows the absolute or rectified value of the signal 160. The trace 166 as shown in FIG. 9(C) shows the output of the short interval, resettable integrator, and the trace 168 as shown in FIG. 9(D) shows the output of the S-H circuit that "reads" the value of the integrator at the end of each short integration period. The recordings are from experiments with a trained monkey, carried out during development of the technologies disclosed here. The time/voltage calibrations are 0.1 sec and 50 microvolts.

D. Third and Later Stages of Signal Processing

A summary of the third and subsequent stages of signal processing is shown in FIG. 10 according to a preferred embodiment of the present invention.

The processed signals 68 from the S-H circuit 86 are digitized by an analog/digital (A/D) signal converter 100 and then fed in parallel to (a) a multi-channel display system 102, and (2) a signal /movement cross correlation and distribution system 101. The display system 102 is an n-cell matrix, where "n" is an integer and each cell 104 in the matrix 102 represents a separate neural data channel. The system 102 provides a quick overview of the pattern of activity across the "n" selected neural recording channels for each of the integration periods described above, and is extremely useful for initially 'focusing in" on those channels that are most active during particular actual or attempted movement. The display system 102 includes a LED display, where the intensity of the LED lighting is a positive function of the

level of neural activity in that channel, or a small computer screen which displays the ongoing level of activity in each channel in the form of color-coded values. Typically, the range of neural activity is divided into eight levels for monitoring purposes, though it is actually digitized for subsequent processing with 12-bit accuracy.

The signal/movement cross correlation and distribution system 101 is preferably a "C" language software routine which performs the following operations as illustrated in FIG. 11 according to a preferred embodiment of the present invention:

(1) Determination of mean signal levels 112 on each channel when the subject is at "rest";

(2) Subtraction of the mean resting signal level 112 for each channel from the ongoing signal 110 of that channel, thus yielding a time-dependent signal D(t) 114 that departs from zero only when a movement is attempted;

(3) Computation of the cross correlations between D(t) 114 and the computerized display 116 of model arm (or joint) position, velocity, or acceleration (see the correlation table in step 2, FIG. 11) as observed by the subject during the calibration procedure described in detail below;

(4) On the basis of these correlations, selection of the channels 118 that will be most useful for control of movements or movement-related parameters of the external device;

(5) Routing/distribution of the selected channels 118 to the artificial neural nets (shown in FIG. 12) that will "shape" that signal for control of particular movements or of any other external device parameter.

Refer now back to FIG. 10. After selection of the subset 118 of channels that will be used to control a particular part of the external device, in this example movements about one of the "joints" in a robot arm, the signals on the channels 118 are fed to a three-layer, software or Artificial Neural Net (ANN) 103 for further processing, before passing to a peripheral device controller 107. After a succession of attempted or actual movements 105, in which each ANN 103 learns to "map" selected neural data channels 118 onto some measured output parameter, the ANNs 103 will thereafter shape the

input signals appropriately for device control. In the case of the paralyzed individual, the output parameter would be a desired or "calibrated" movement of the arm, or movement about a major joint in the arm, that (s)he observes on a computer display and "tries" to emulate with his/her own paralyzed arm. This "calibration" procedure is described in more detail in the next section.

The properties of a current ANN 103 used for this purpose are depicted in FIG. 12. The preprocessed neural signals 120, with resting back-ground levels removed, are fed from the particular neural channels 118 selected for control of wrist movements of a robot arm to each input node of a software ANN 103. The ANN 103 has a standard three layer, feedforward network that is trained using back propagation with momentum. The first layer contains three input nodes 122, the second, hidden layer contains five nodes 124, and the output layer has a single node 126 (scalar output). All of the nodes are fully interconnected in a strictly feedforward manner; i.e., each node in a layer is fully interconnected in a feedforward manner to every node in the next layer, and only to those in the next layer. For instance, each input node 122 receives input data 120 from all of the selected channels 118, it then sends an output to each node 124 in the middle or hidden layer. Each node 124 in the hidden layer receives inputs from each of the nodes 122 in the input layer. In turn, all nodes 124 in the hidden layer send outputs to the single node 126 in the final or ANN output layer. To further smooth out data transients that are outside of the control frequencies of interest (0-5 Hz), each data point fed to the ANN 103 comprises a running average of the current value of the neural signal in channel "m" (at time "t") plus the previous nine values of that signal (from time t-1 to t-9). This averaging period was determined by trial and error and may be changed to other values.

An example of the success of this three-layer net in mapping two channels of neural data onto a simultaneously obtained measure of an alert monkey's wrist position, according to a preferred embodiment of the present invention, is shown in FIGS. 13(A) and 13(B). Referring first to FIG. 13(A), top two traces 130 and 132 show processed multiunit activity (outputs of S-H circuits) from two channels, identified as channel 3 and channel 14

respectively, of a 36-electrode array implanted in the left motor cortex of a trained monkey, recorded as the animal flexed and extended his right wrist. Actual wrist position is shown by a third trace 134. Channel 3 shows a peak change in activity leading wrist extension, with a smaller elevation during wrist flexion. Channel 14 shows a large increase in activity leading and during wrist flexion, and a moderate increase during extension. Referring now to FIG. 13(B), output 138 of the ANN 103, which in this case is the position of the animal's wrist predicted from activity in neural channels 3 and 14, is shown by the heavy trace adjacent to an offset lighter movement trace 136 which shows his actual wrist position. Note the good correspondence, even though only two neural channels were used to compute predicted wrist position 138. The movement trace 136 is not the same as that shown in the previous trace 134, but was computed and recorded later, during training of the ANN 103. After the ANN 103 was trained over 10 movement trials, the match between actual and predicted wrist position attained a correlation of r = 0.96. Use of the ANN 103 output 138 to drive a robot "wrist" produced a robot wrist movement trace indistinguishable from the ANN 103 output 138.

Finally, referring back to FIG. 10, the output 138 of each neural net 103 is fed to an interface controller 107. An interface controller is a device which converts the output signals from one system into an appropriate set of signals for controlling some other system or device and known to persons skilled in the art. Interface controller 107 comprises a microprocessor which is programmed to convert the output of the neural net 103 into the voltages and currents that is necessary for actuating, for example, the robot controller, and thus moving the robot's wrist.

E. Calibration and Use of the System

FIG. 14 shows steps that are followed by a paralyzed individual in setting up, calibrating, and using a neurally control external device according to a preferred embodiment of the present invention. Here the control of an artificial limb, or of stimulation of paralyzed muscles of the limb, to produce a particular motion is used as a particular example. It is assumed in this

description that two prior conditions have been met. First, the electrodes have been implanted in brain regions that have been shown with functional imaging procedures to be under the subject's voluntary control; i.e., which are "activatable" by the subject when desired. If possible, they should also be implanted in a brain region that is normally activated when the subject attempts one or more of the particular movements that the prosthetic device will be asked to generate, though this is not an absolutely necessary requirement. Second, a prosthetic specialist will have already set channel gains and other parameters after device implantation. Each day or at selected intervals thereafter, the patient/subject would perform the following calibration routine.

First, (s)he learns to use a particular, monitored biological signal to turn on the system calibration computer when desired. If eye movements are intact, this signal could be a patterned sequence of eye blinks, sensed by a small monitoring device, that would not occur normally. If control of certain neck or facial muscles remains, their electromyographic activity could be used in the same coded way. In a totally paralyzed patient, the signal could be a particular time code of brain activity, generated voluntarily by the patient but unlike that which would occur during normal operation of the external device. A similar set of signals can be used for turning the calibration system off, or later, for turning the device to be controlled on or off when the neural control system has been calibrated.

Second, with the assistance of another person or again using a coded sequence of biological signals, the subject selects a particular movement for calibration from a predetermined list. The list may have the following options: alternate flexion and extension of the elbow; flexion-extension of the wrist; movements about the shoulder; grasping and releasing of an object; reaching to different points in space; or some combination of these.

When the subject gives a "ready" signal, the selected movement is displayed on a video monitor, simulated by animation or a video record of a model performing an actual movement. The model movement is performed at a slow to moderate speed and, during its performance, the subject "tracks"

the observed movement by attempting to move his/her own paralyzed limb in exactly the same manner and at the same speed. "N/2" repetitions would be performed, where N is a non-zero even integer. During these repetitions, the system (a) cross correlates the neural signals with the model movement(s) or some selected parameter (e.g., position, velocity, acceleration) of that movement; and (b) on the basis of the average of these correlations over the N/2 repetitions, determines which subset of neural channels was most highly correlated with the model movement and its parameters. The activity on the selected subset channels would then (c) be routed to the ANNs 103 which control the components of the external device that will produce a movement like the model movement. Another N/2 repetitions are then performed, and the appropriate ANNs 103 (d) "map" these selected neural inputs onto a stored record of parameter values for the model movement.

The subject now performs this same procedure for the next movement in the set, and the four steps (a) through (d) are repeated for that movement. And so on, until the entire calibration procedure has been performed. This procedure is performed daily or only at needed intervals (when the subject notices a diminution in control accuracy), with the optimal neural channels being re-selected at each calibration procedure and mapped again onto the desired movement functions. Thus, this periodic calibration procedure adapts to or allows compensation for changing neural signal parameters, and it ensures the optimal selection of those channels that are still useful at any time for device control.

Please note also that the subject's own brain can also adapt to changing signal properties and the challenges that these changes impose on device control. That is, if the subject can voluntarily activate the brain region from which signals are monitored and can vary these signal levels, then (s)he can learn to modulate these activation levels so that the external device can still be manipulated, even if there is drift or other unknown changes in the activity of the recorded neural channels.

Obviously, many modifications and variations of the present invention are possible to persons skilled in the art, without departing from the spirit and

the scope of the invention disclosed herein. It is to be understood, therefore, that the invention can be practiced otherwise than as specifically described.

CLAIMS

What is claimed is:

1. A device for collecting multicellular signals directly from a nervous system and transmitting the signals to an external receiver, comprising:

A) a plurality of electrodes formed in bundles of flexible wires with tips at staggered length aligned to be implanted in the nervous system for collecting multicellular signals; and

B) a signal processing mechanism connected to the electrodes for multiplexing and transmitting the signals from the electrodes to the external receiver.

2. The device according to claim 1, wherein the number of the flexible wires in a bundle ranges from 3 to 10.

3. The device according to claim 1, wherein the diameter of the flexible wires is smaller than 50 em.

4. The device according to claim 1, wherein the difference in length from one tip to its neighbor tip of the wires is variable.

5. The device according to claim 4, wherein the difference in length from one tip to its neighbor tip of the wires is about 0.3 to 0.6 mm.

6. The device according to claim 1, wherein the flexible wires in a bundle are made from noble metal.

7. The device according to claim 1, wherein the signal processing mechanism comprises:

A) an insulating substrate;

B) an array of electrode contact pads mounted on the substrate for receiving the electrodes, each electrode received individually by one of the electrode contact pads, and with the electrode contact pads being electrically isolated from each other at the substrate;

C) a microchip bonded in close contact with the substrate for receiving and multiplexing the signals from the electrodes; and

D) an electric connection to the microchip for relaying power to the microchip and transmitting the signals received at the microchip to the external receiver.

8. The device according to claim 7, wherein the electric connection is a hardware device.

9. The device according to claim 8, wherein the hardware device is a cable.

10. The device according to claim 7, wherein the electric connection is a wireless device.

11. The device according to claim 10, wherein the wireless device is a nonresonant wireless setup.

12. The device according to claim 11, wherein the nonresonant wireless setup comprises:

A) a first coil in connection with the microchip for relaying power to the microchip; and

B) a second coil in connection with the microchip for receiving and transmitting the multiplexed signals to the external receiver.

13. The device according to claim 10, wherein the wireless device is a resonant wireless setup.

14. The device according to claim 13, wherein the resonant wireless setup comprises:

A) a coil in connection with the microchip for relaying power to the microchip; and

B) a low pass filter in connection with the microchip for receiving and transmitting the multiplexed signals to the external receiver.

15. The device according to claim 7, wherein the microchip comprises signal processing integrated circuits.

16. An apparatus for recording multi-neuron signals directly from a nervous system comprising a plurality of sensors, wherein each sensor further comprises a bundle of noble metal wires with tips at staggered length.

17. An apparatus for recording multicellular signals directly from small clusters of neurons and broadcasting the signals to an external receiver, comprising:

A) an array of electrodes for receiving the signals;

B) a signal processor for multiplexing and transmitting the signals to the external receiver, wherein the signal processor comprises:

i) an insulating substrate;

ii) an array of electrode contact pads mounted on the substrate for receiving the electrodes, each electrode received individually by one of the electrode contact pads with the electrode contact pads being electrically isolated from each other at the substrate;

iii) a microchip bonded in close contact with the substrate for receiving and multiplexing the signals from the electrodes, wherein the microchip comprises signal processing integrated circuits; and

iv) a electric device connected to the microchip for relaying power to the microchip and carrying the signals from the microchip to the external receiver.

18. The apparatus according to claim 17, wherein the electrodes are formed in a bundle of noble metal wires with tips at staggered length.

19. The apparatus according to claim 17, wherein the electric device is a hardware connection.

20. The apparatus according to claim 19, wherein the hardware connection is a cable.

21. The apparatus according to claim 17, wherein the electric device is a wireless connection.

22. The apparatus according to claim 21, wherein the wireless connection is a nonresonant wireless setup.

23. The apparatus according to claim 22, wherein the nonresonant wireless setup comprises:

A) a first coil in connection with the microchip for relaying power to the microchip; and

B) a second coil in connection with the microchip for receiving and transmitting the multiplexed signals from the microchip to the external receiver.

24. The apparatus according to claim 21, wherein the wireless connection is a resonant wireless setup.

25. The apparatus according to claim 24, wherein the resonant wireless setup comprises:

A) a coil in connection with the microchip for relaying power to the microchip; and

B) a low pass filter in connection with the microchip for receiving and transmitting the multiplexed signals from the microchip to the external receiver.

26. An instrument for collecting multicellular signals directly from a nervous system and transmitting the signals to an external receiver, comprising:

A) at least one sensor for receiving the signals, wherein the sensor comprising:

i) a bundle of wires with staggered length in an array, wherein each wire has a tip for receiving the signals from the nervous system; and

ii) an optical cement bead through which the wires may pass for holding the wires in position in a selected distance from the most distant wire tip; and

B) a signal processor connected to the sensor for multiplexing and transmitting the signals from the sensor to the external receiver.

27. The instrument according to claim 26, wherein the selected distance is about 6-8 mm.

28. The instrument according to claim 26, wherein the wires are made from conductive materials.

29. The instrument according to claim 28, wherein the conductive materials are noble metal.

30. A method for using multicellular signals collected directly from a nervous system to control an external device comprising the steps of:

A) collecting multicellular signals directly from a nervous system;

B) multiplexing and broadcasting the signals to an external receiver;

C) receiving the signals for demultiplexing and separating the signals;

D) rectifying the signals; and

E) converting the signals logarithmically.

31. The method according to claim 30, further comprising the steps of:

F) integrating the log rectified signals over a short time period;

G) sample-hold reading of the peak value of the integral for generating a S-H output; and

H) using the S-H output for controlling the external device.

32. A channel display system for monitoring recorded multicellular signals, comprising:

A) a device for recording multichannel neural signals directly from a nervous system and broadcasting the signals;

B) an external receiver for receiving the signals;

C) electric connection means for connecting to an external receiver to relay the signals; and

D) a visual display for displaying the signals in a matrix, wherein each cell of the matrix represents a separate neural data channel.

33. The channel display system according to claim 32, wherein the visual display comprises an LED, wherein the intensity of illumination of the LED is a positive function of the level of neural signals fed from the related neural data channel.

34. The channel display system according to claim 32, wherein the visual display comprises a computer screen, wherein the color of each cell of the display matrix on the screen is coded according to the level of neural signals fed from the related neural data channel.

35. A method for using multicellular signals collected directly from a nervous system to control a prosthetic device comprising the steps of:

A) using a detective device with a plurality of electrodes to record multicellular signals directly from a nervous system;

B) multiplexing and broadcasting the signals to an external receiver;

C) processing the signals;

D) converting the signals in digital form; and

E) displaying the signals in a multi-channel visual display where the display in one channel correlates to signals collected from one electrode.

36. A method for using multicellular signals collected directly from a nervous system to control a device comprising the steps of:

A) setting up a calibration routine for a subject's learning of a movement;

B) developing a model for that movement;

C) using a detective device with a number of electrodes to record multicellular signals directly from the subject's nervous system, wherein one electrode represents one signal channel;

D) multiplexing and broadcasting the signals to an external receiver;

E) processing the signals;

F) converting the signals in digital form;

G) determining of mean signal levels over a period of 10 to 20 seconds for each channel where signals in one channel correlates to signals collected from one electrode when the subject is at rest;

H) subtracting the mean resting signal level for each channel from the signals recorded at different time to yield a signal as a function of time, D(t), that departs from zero only when a movement is attempted;

I) computing the cross correlation between D(t) and the computerized model of the attempted movement in terms of at least one motion parameter; and

J) selecting the neural channels which are useful for controlling the device or a component of the device based on the cross correlation calculation.

37. The method according to claim 36, further comprising the step of:

K) distributing the selected channels to neural nets for shaping the signals for control of the movement of the device.

38. The method according to claim 36, wherein the motion parameters are position, velocity, and acceleration.

39. An apparatus for collecting multicellular signals directly from a nervous system to control an external device, comprising:

A) sensors in an array for recording the signals;

B) a transmitter for broadcasting the signals;

C) a processor for receiving the signals, converting the signals logarithmically, and integrating the signals to generate a S-H output in analog form;

D) a converter for converting the signals in analog form into digitized signals;

E) a computing interface for performing neural signal/model movement cross correlation to select the signals that are most useful for control of a particular movement of the device and distributing the selected signals;

F) a microcomputer for supporting a feedforward neural network for receiving the selected signals and mapping the signals onto a model movement to generate control parameters; and

G) an interface controller for controlling the device to make movement same or similar to the model movement according to the control parameter.

40. A method for using a neural net to map neural signals onto desired movement or control parameters to control a device comprising the steps of:

A) recording neural signals in multichannels directly from a subject's nervous system;

B) removing resting background levels from the signals;

C) calculating a running average for each data point of the signals at time "t" in channel "m" by combining the previous several values of that signal;

D) feeding the signals from the particular channels selected according to the desired movement or control parameters in a feedforward direction to each input node of the neural net, wherein the neural net has at least three input nodes, and all the nodes are fully interconnected; and

F) outputting the signals from the neural net to a peripheral device controller.

41. A method for calibrating a neutral control system comprising the steps of:

A) turning on the control system;

B) selecting a model movement for calibration;

C) giving ready signal to the system;

D) displaying the selected model movement on a visual display;

E) allowing a subject to attempt to track or emulate the selected model movement;

F) recording neural signals from a number of neural channels of the subject during the attempted movement;

G) comparing the recorded neural signals with the selected model movement by correlation methods, so that the neural channels whose activity is most highly correlated with the attempted movement may be selected by the system;

H) repeating steps E) to G) for N/2 times, wherein N is a number equal to or greater than one; and

I) performing another N/2 repetitions of E) to G) to allow a neural net to map the recorded neural signals from the selected channels onto a set of parameters for the selected model movement.

42. A movement calibration system comprising:

A) a biological signal monitor for turning on or off the system;

B) a database for storing optimal parameters related to a family of model movements a subject attempts to make;

C) a visual display for displaying a movement selected from the database; and

D) a computer for matching the selected movement and the subject's attempted movements by calculating their correlation.

43. A method for using multicellular signals collected directly from a nervous system to control a prosthetic device comprising the steps of:

A) setting up a calibration routine for a subject's learning of a desired movement;

B) computerizing a "model" for that desired movement;

C) using a detective device with a number (n) of electrodes to record multicellular signals directly from the subject's nervous system when the subject attempts the desired movement, wherein each of the n electrodes represents one signal channel;

D) multiplexing and broadcasting the signals to an external receiver;

E) processing the signals for generating signals in analog form;

F) converting the signals into digital form;

G) determining of mean signal levels for each channel where signals in one channel correlates to signals collected from one electrode when the subject is at "rest";

H) subtracting the mean resting signal level for each channel as computed in step (G) from the collected ongoing signal to yield a signal as a function of time, D(t), that departs from zero only when a movement is attempted by the subject;

I) computing the cross correlation between D(t) and the computerized model of the desired movement in terms of kinetic parameters such as position, velocity, and/or acceleration;

J) selecting the neural channels which are most useful for controlling the device or a component of the device based on the cross correlation calculation; and

K) distributing of the selected channels to neural nets to shape the signals for controlling the device to produce a movement as same or similar to the desired movement.

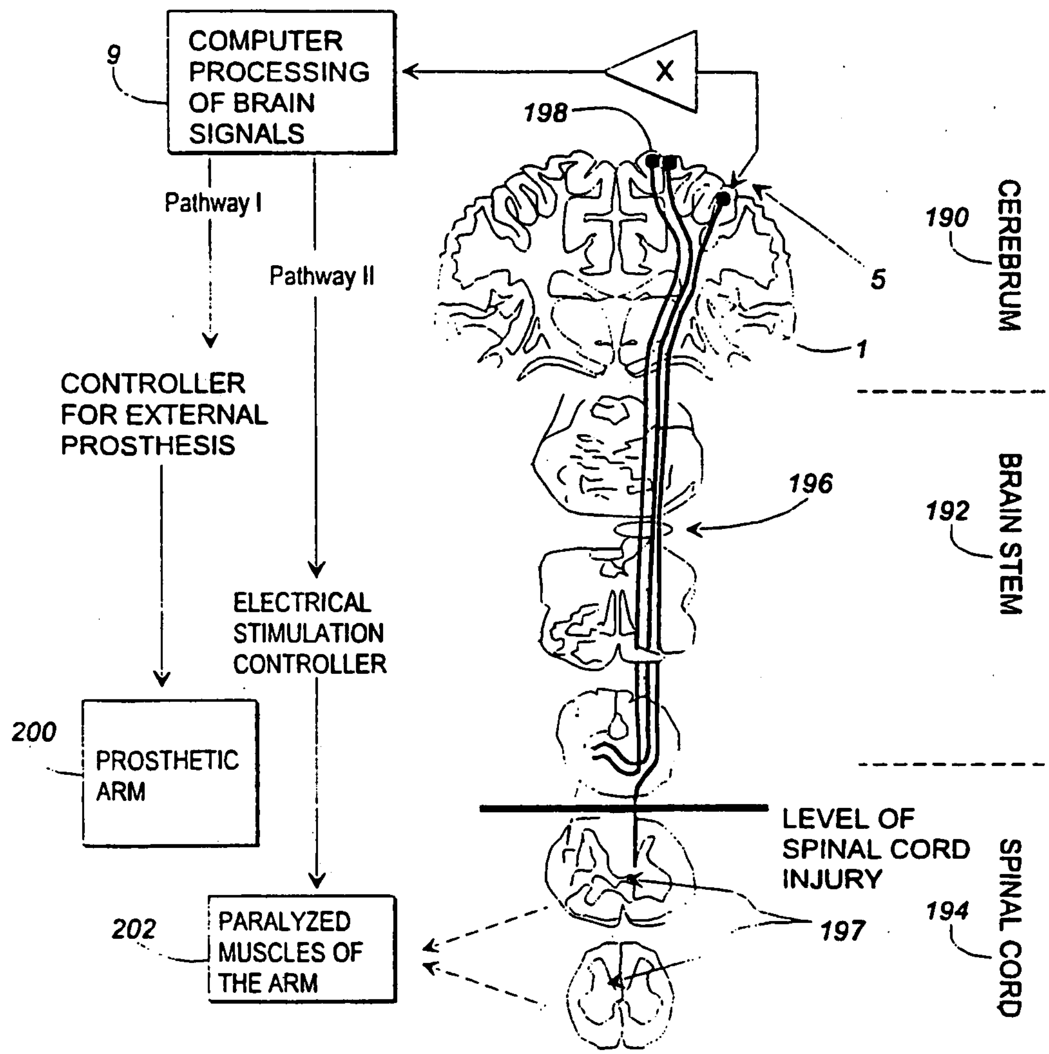

COMPUTER PROCESSING OF BRAIN SIGNALS
9
X
198
5
1
190
CEREBRUM
Pathway I
Pathway II
CONTROLLER FOR EXTERNAL PROSTHESIS
196
192
BRAIN STEM
ELECTRICAL STIMULATION CONTROLLER
200
PROSTHETIC ARM
LEVEL OF SPINAL CORD INJURY
194
SPINAL CORD
197
202
PARALYZED MUSCLES OF THE ARM

FIG. 1

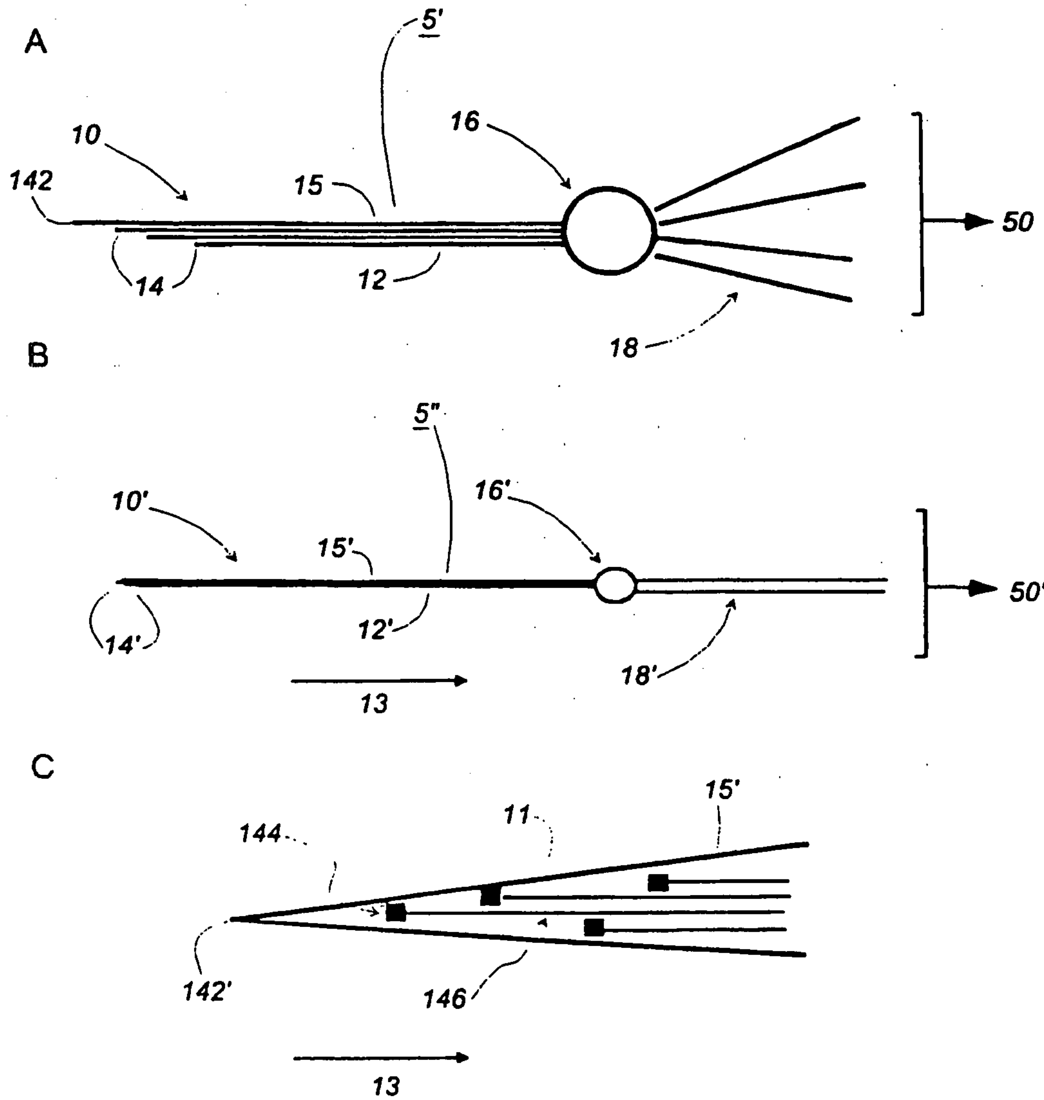

A
5'
10
16
142
15
50
14
12
18
B
5"
10'
16'
15'
50'
14'
12'
18'
13
C
15'
11
144
142'
146
13

FIG. 2

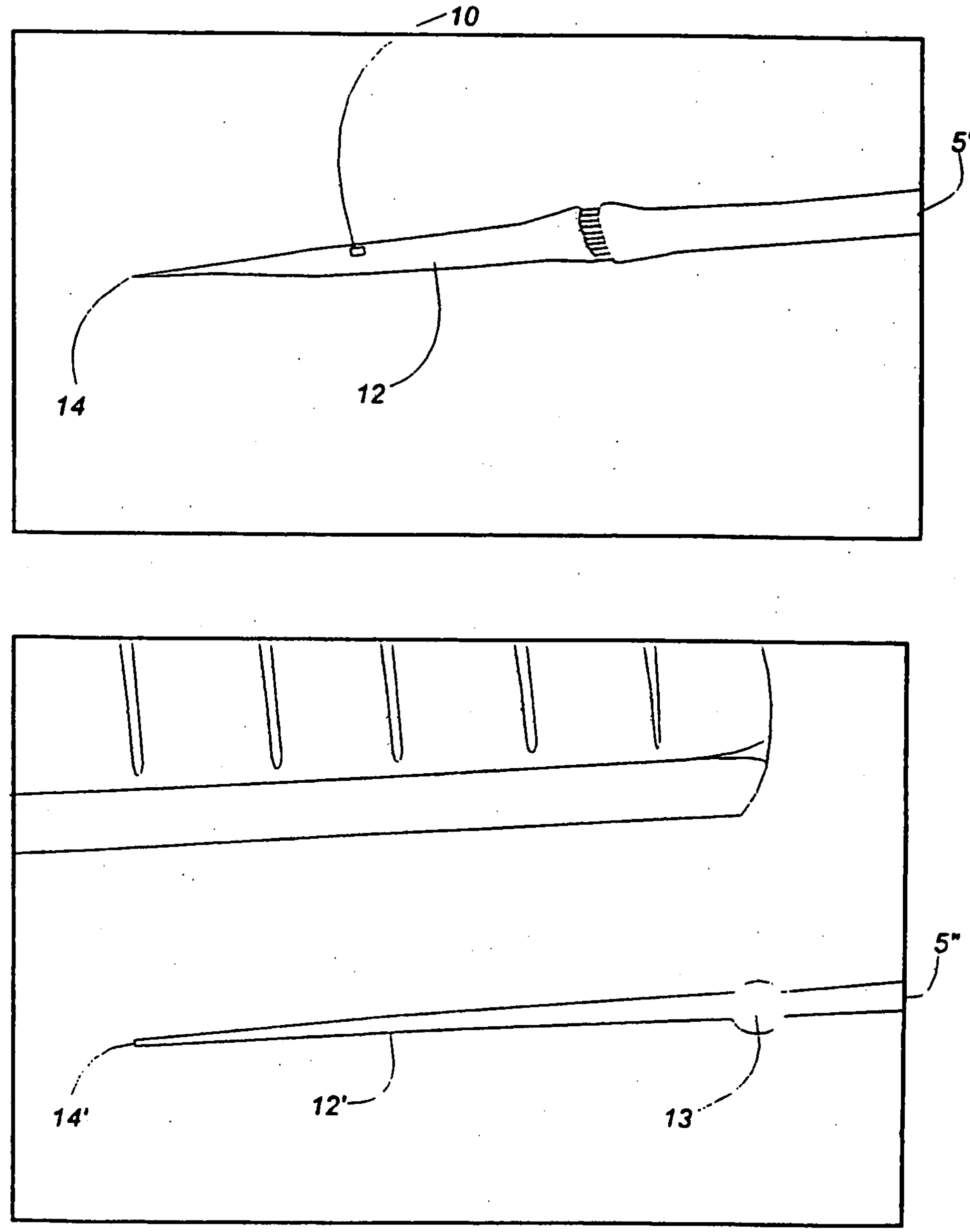


FIG. 3

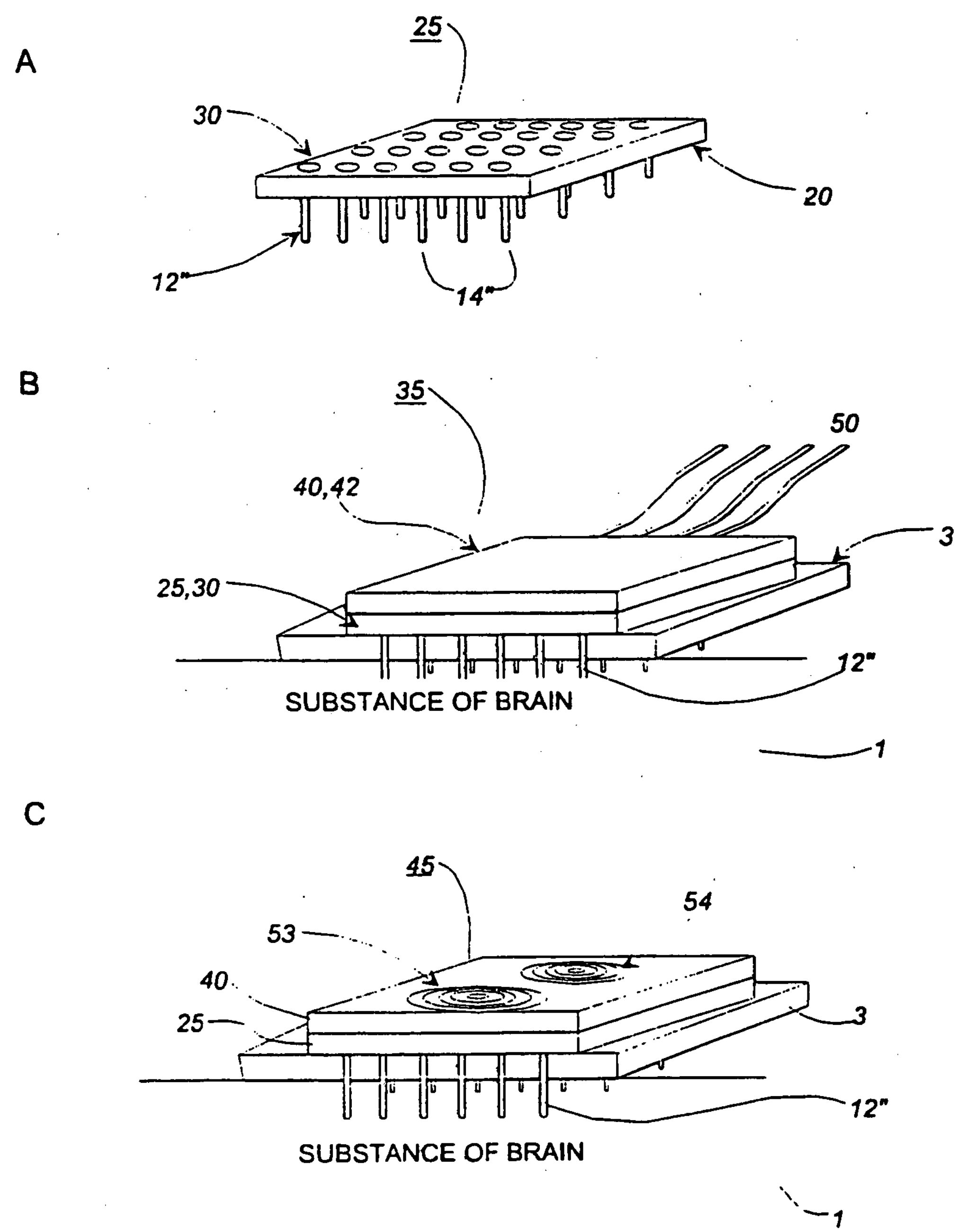

A
25
30
20
12"
14"
B
35
50
40,42
3
25,30
12"
SUBSTANCE OF BRAIN
1
C
45
54
53
40
25
3
12"
SUBSTANCE OF BRAIN
1

FIG. 4

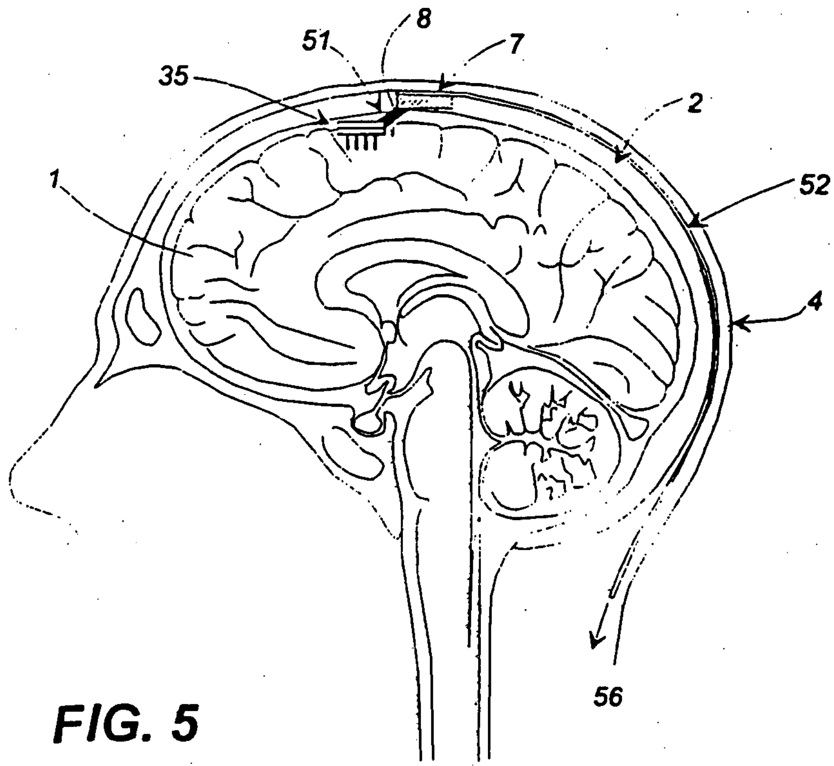


FIG. 5

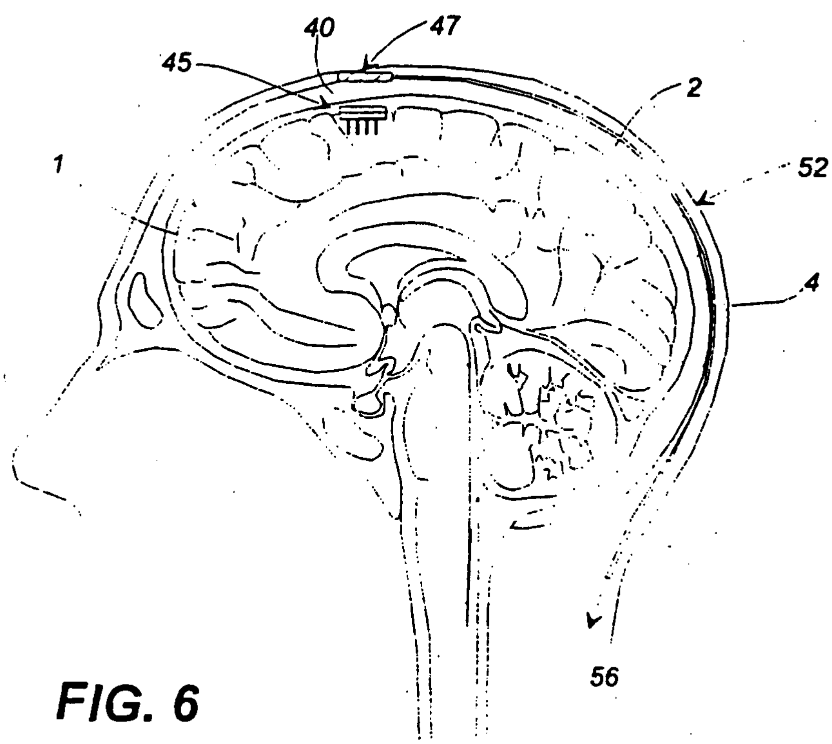


FIG. 6

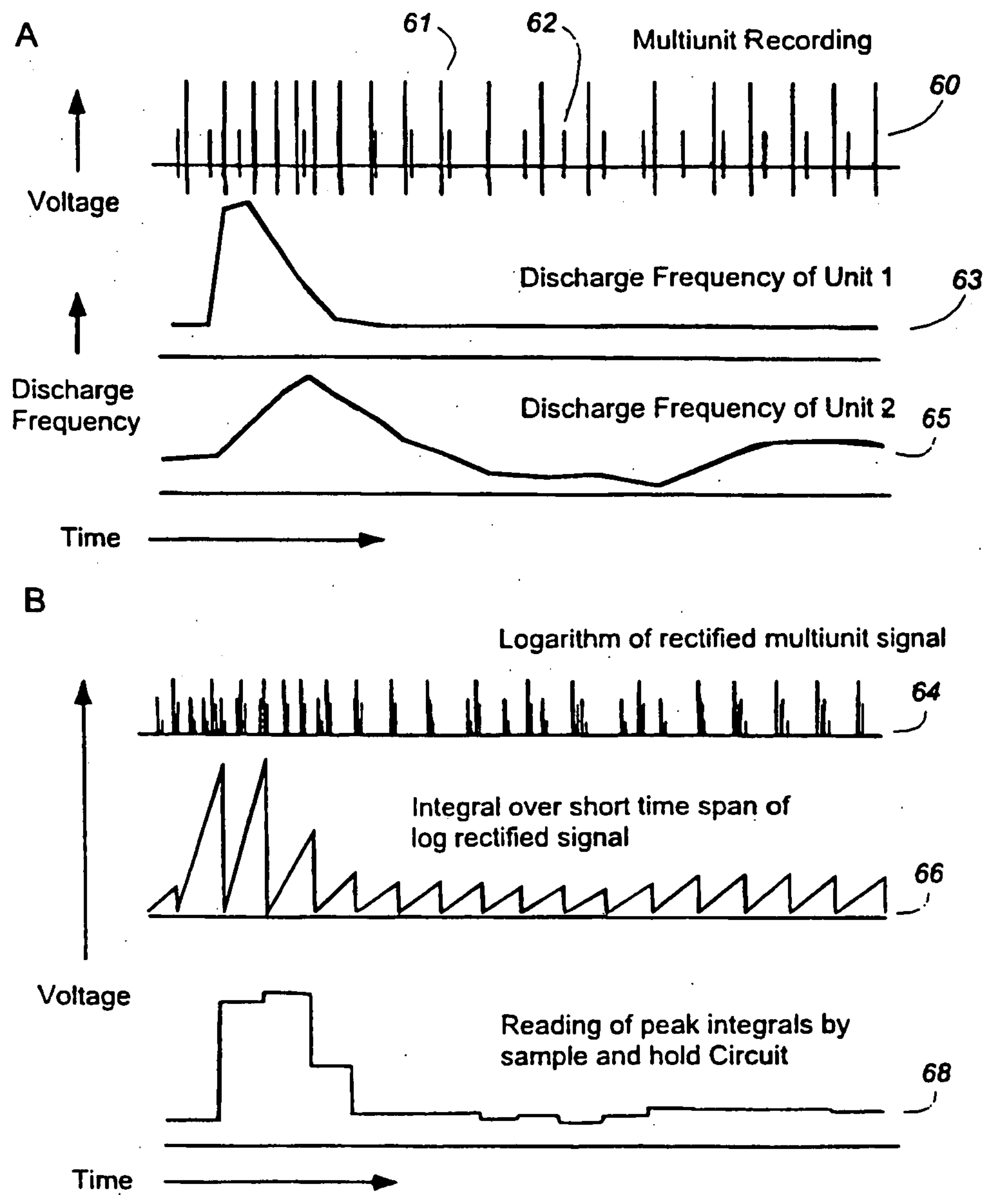

A
61
62
Multiunit Recording
60
Voltage
Discharge Frequency of Unit 1
63
Discharge Frequency
Discharge Frequency of Unit 2
65
Time
B
Logarithm of rectified multiunit signal
64
Integral over short time span of log rectified signal
66
Voltage
Reading of peak integrals by sample and hold Circuit
68
Time

FIG. 7

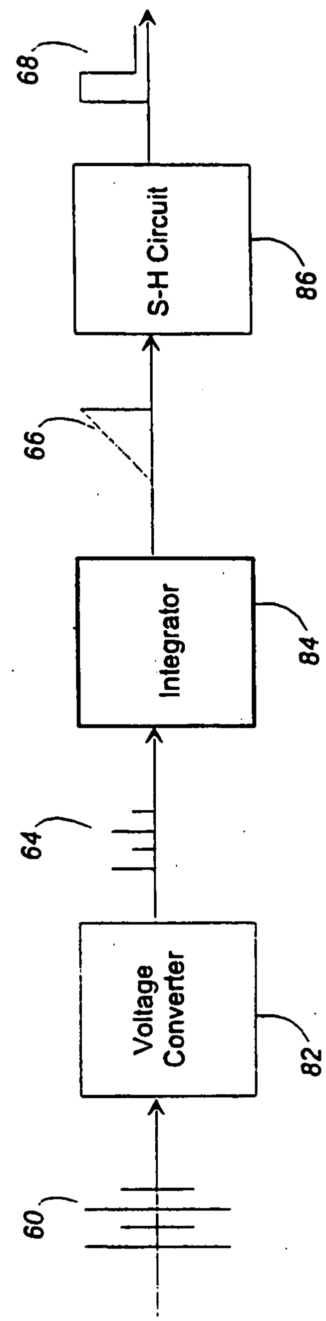


FIG. 8

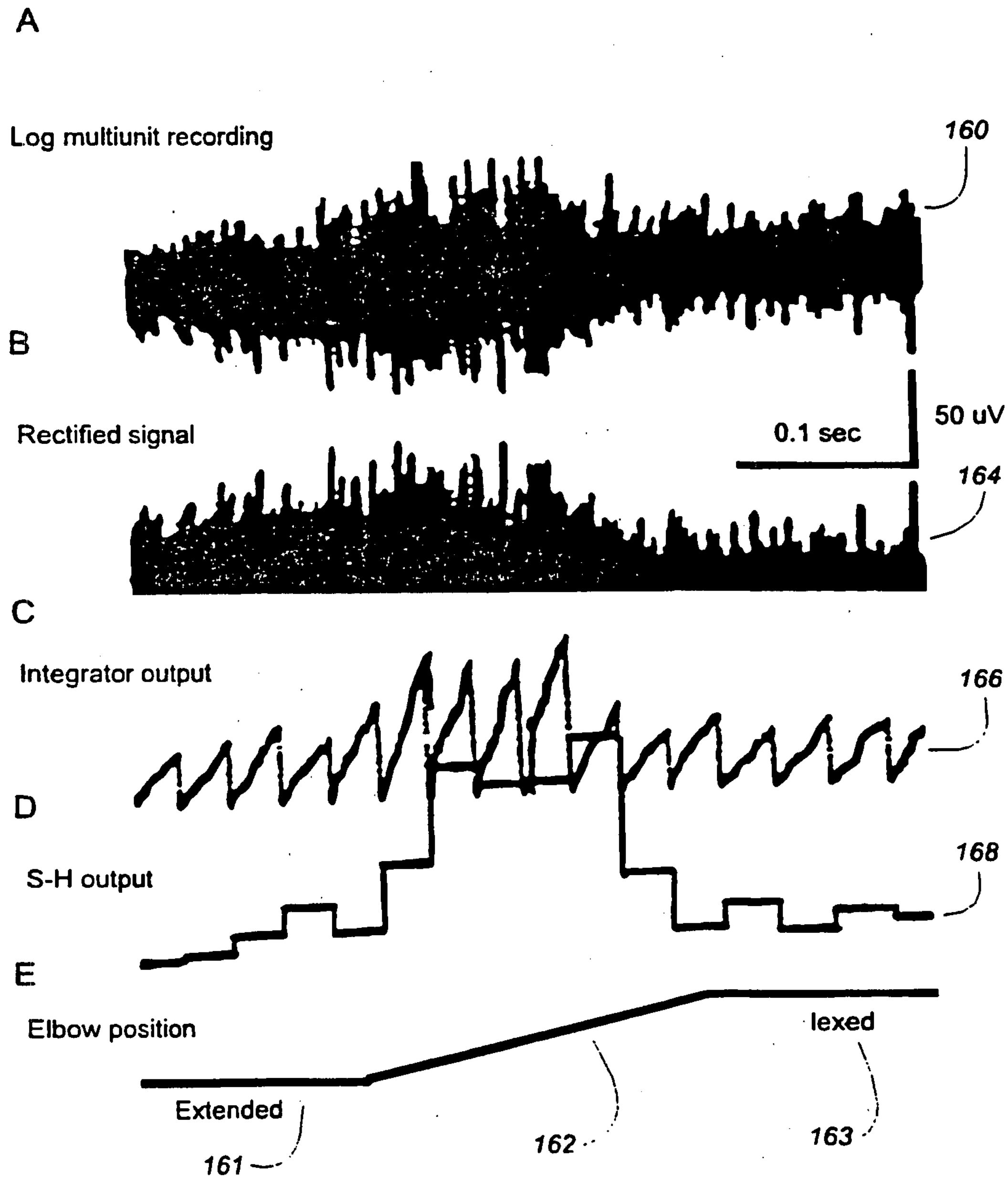

A
Log multiunit recording
160
B
Rectified signal
0.1 sec
50 uV
164
C
Integrator output
166
D
S-H output
168
E
Elbow position
lexed
Extended
161
162
163

FIG. 9

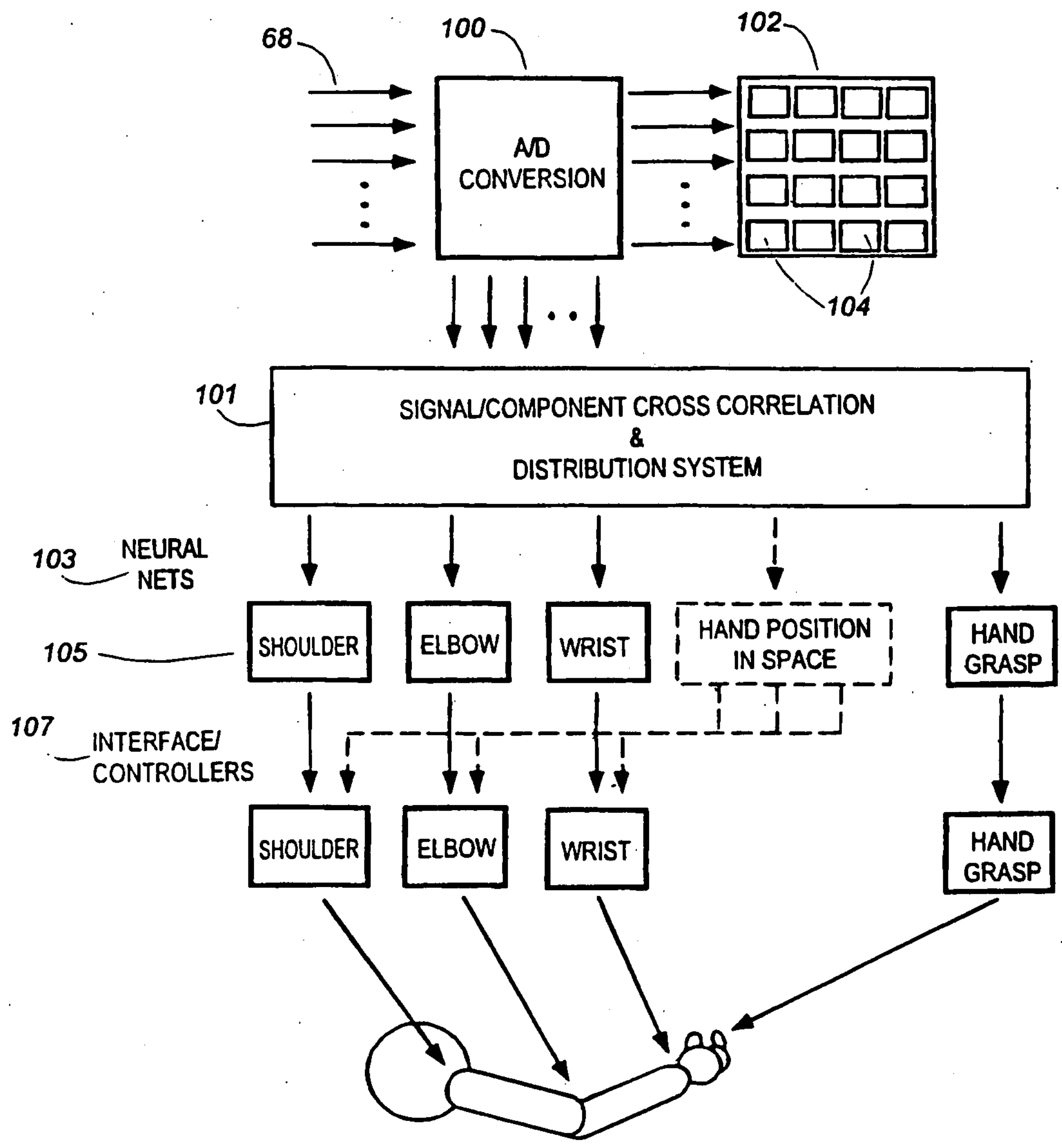
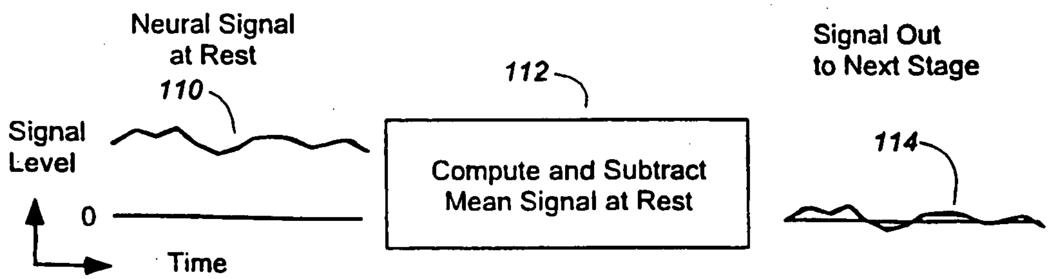

68
100
102
A/D
CONVERSION
104
101
SIGNAL/COMPONENT CROSS CORRELATION
&
DISTRIBUTION SYSTEM
103
NEURAL
NETS
105
SHOULDER
ELBOW
WRIST
HAND POSITION
IN SPACE
HAND
GRASP
107
INTERFACE/
CONTROLLERS
SHOULDER
ELBOW
WRIST
HAND
GRASP

FIG. 10

STEP 1



STEP 2

ATTEMPTED MOVEMENT 116

NEURAL CH	1	2	3	• •
1	0.8	0.2	-0.7	
2	-0.2	0.8	0.0	
3	0.7	0.4	0.5	
4	0.6	-0.3	0.9	
5	0.0	0.7	-0.1	
6	0.1	0.6	0.5	

MOVEMENT	CHANNELS SELECTED 118
1	1,3,4
2	2,5,6
3	1,4

FIG. 11

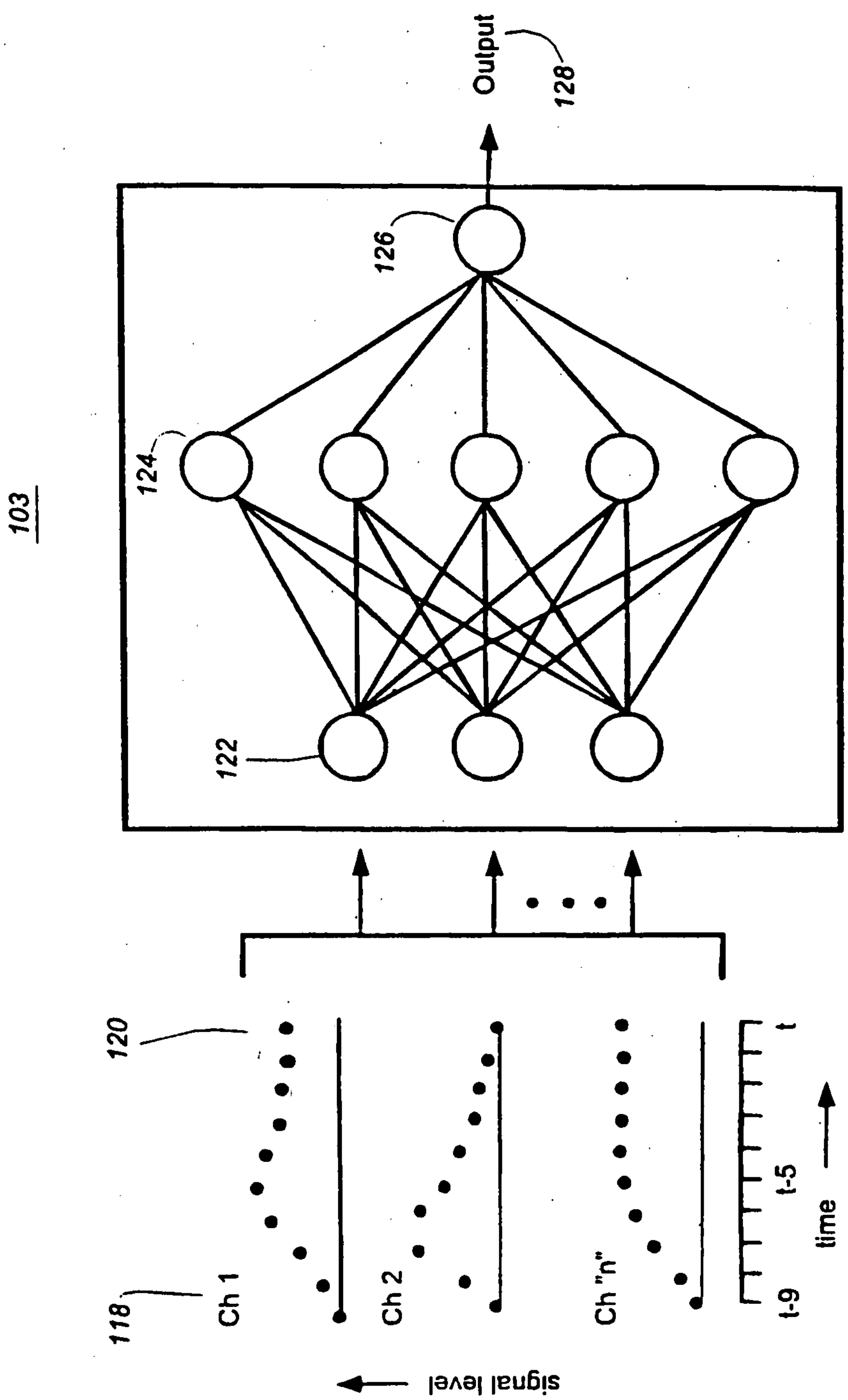

Output
128
126
124
122
103
120
118
Ch 1
Ch 2
Ch "n"
t-9
t-5
t
time
signal level

FIG. 12

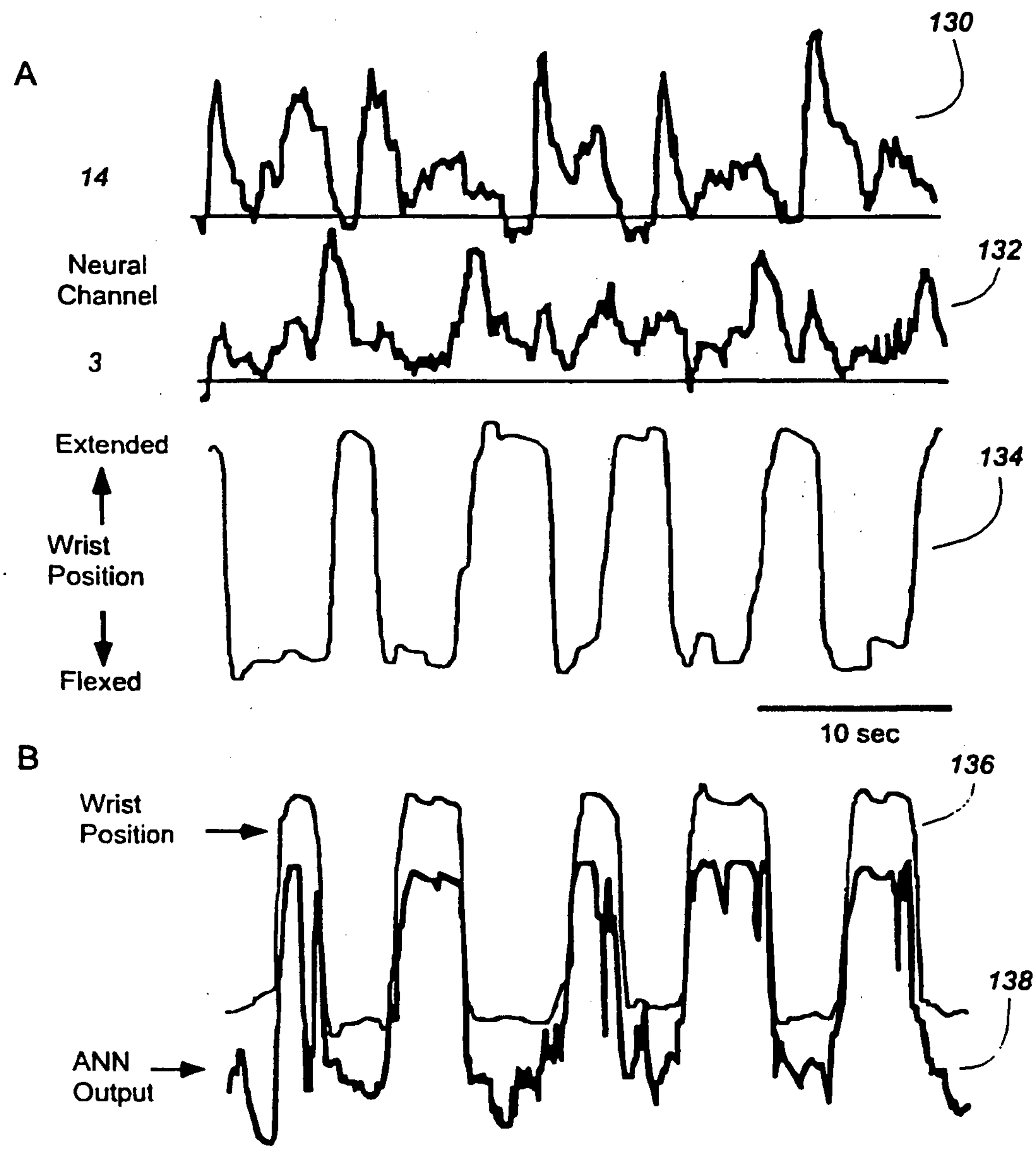
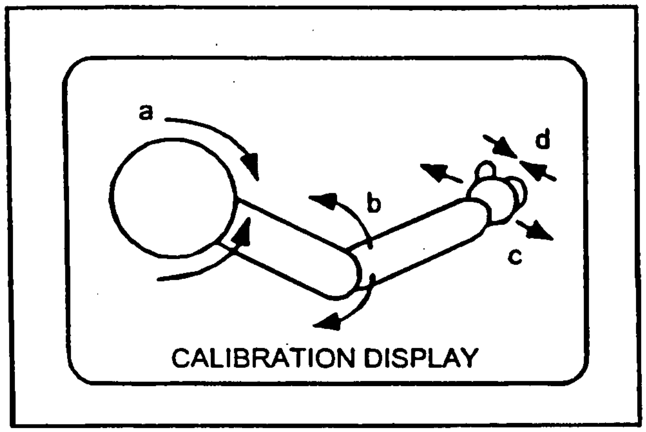

A
130
14
Neural
Channel
132
3
Extended
134
Wrist
Position
Flexed
10 sec
B
136
Wrist
Position
138
ANN
Output

FIG. 13

SYSTEM CALIBRATION METHOD



TURN ON CALIBRATION SYSTEM

SELECT MOVEMENT FOR CALIBRATION (a,b,...)

GIVE READY SIGNAL

ATTEMPT TO "TRACK" MOVEMENT

'N' MOVEMENTS ?

YES NO

LAST MOVEMENT TO BE CALIBRATED ?

YES NO

NEXT MOVEMENT

END CALIBRATION

FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18172

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61B 5/04
US CL :600/372, 378
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 600/372, 373, 377, 378, 383, 544, 546; 607/48, 49, 62, 116,-118; 606/130

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,178,161 A (KOVACS) 12 January 1993, entire document.	7-9, 15, 17, 19, 20, 35 --- 10-14, 16, 18, 21-25, 36, 37, 42
X --- Y	US 5,524,338 A (MARTYNIUK et al.) 11 June 1996, entire document.	1-6, 26, 28, 29 --- 16, 18, 27
X	US 5,413,103 A (ECKHORN) 09 May 1995, entire document.	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 NOVEMBER 1999	23 DEC 1999

Name and mailing address of the ISA/US	Authorized officer
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Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18172

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,279,305 A (ZIMMERMAN et al.) 18 January 1994, entire document.	10-14, 21-25
A	US 5,638,826 A (WOLPAW et al.) 17 June 1997, entire document.	1-43
A	US 5,215,088 A (NORMANN et al.) 01 June 1993, entire document.	1-43
A	US 5,692,517 A (JUNKER) 02 December 1997, entire document.	1-43